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FINAL REPORT ON THE OECD PILOT PROJECT TO COMPARE PESTICIDE DATA REVIEWS

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ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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Foreword

This Environment Monograph presents the findings and recommendations of the OECD "Pilot Project" to Compare Pesticide Data Reviews. The Pilot Project was carried out as part of the work of the OECD Pesticide Programme. It was initiated at the request of OECD countries during a pesticide re-registration workshop in Washington, D.C. in October 1992. These countries saw both a need and an opportunity to increase international co-operation in re-registration of old pesticides. The project's purpose was to determine the extent to which countries might share the burden of pesticide data review by using each other's data review reports, rather than separately evaluating the same pesticides.

The Pilot Project began by examining existing data review reports on a select group of pesticides in order to compare how different countries and international organisations had evaluated the same or similar data on health and environmental effects. The extent to which existing reports might already be used to complement or replace a separate national review was then considered. Finally, ways to increase exchange and use of reports among OECD countries in the future were recommended.

The Pilot Project included seven pesticides known to have been reviewed by multiple countries and/or international organisations: amitraz, diazinon, dicofol, dinocap, endosulfan, iprodione, and pyridate. For each of these pesticides, the project compared countries' reviews in the test areas of toxicology, ecotoxicology and environmental fate, with a less detailed analysis in the area of physical-chemical properties. The project focused exclusively on data review *reports*, not on the original pesticide *data*, in order to avoid infringement of industry rights with regard to confidential business information.

The principal finding of the Pilot Project was that mutual use of pesticide data review reports among OECD Member countries, and co-operation in re-registration, could begin immediately. Although there are considerable differences among existing reports, it was found that many could usefully *complement* another country's independent review. Moreover, it was found that in certain areas – where study results are straightforward and countries' analyses are consistent – existing reports could already be used in lieu of a separate national review.

The Joint Meeting of the Chemicals Group and Management Committee recommended that this report be derestricted. It is being published on the responsibility of the Secretary-General of the OECD.

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Executive Summary

This report presents the findings and recommendations of the OECD "Pilot Project" to Compare Pesticide Data Reviews. The Pilot Project was initiated at the request of OECD Member countries who saw both a need and an opportunity to increase international co-operation in the re-registration of old pesticides. The purpose of the Pilot Project was to determine the extent to which countries might ***share the burden of pesticide data review*** by using each other's data review reports, rather than separately evaluating the same pesticides.

The Pilot Project began by examining existing data review reports on a select group of pesticides in order to compare how different countries and international organisations had evaluated the same or similar data on health and environmental effects. The project then considered the extent to which existing reports might already be used to complement or replace a separate national review. Finally, the project recommended ways to increase the exchange and use of reports among OECD countries in the future.

The Pilot Project included seven pesticides known to have been reviewed by multiple countries and/or international organisations. These were amitraz, diazinon, dicofol, dinocap, endosulfan, iprodione and pyridate. For each of these pesticides, the project compared countries' reviews in the test areas of toxicology, ecotoxicology and environmental fate, with a less detailed analysis in the area of physical-chemical properties. The project focused exclusively on the data review ***reports***, and not on the original pesticide ***data***, in order to avoid infringement of industry rights with regard to confidential business information.

The principal work of the Pilot Project was done by seven OECD countries who volunteered to take a lead role in analysing and comparing available data review reports on the seven pesticides. Three other countries and two international organisations also participated in the project by submitting their data review reports for analysis and by commenting on draft documents written by the lead countries. The table below shows the lead country and participants for each Pilot Project pesticide.

The principal finding of the Pilot Project was that mutual use of pesticide data review reports among OECD countries, and co-operation in re-registration, could begin immediately. Although there are considerable differences among existing reports, the project found that many could usefully ***complement*** another country's independent review. Moreover, the project found that in certain areas – where study results are straightforward and countries' analyses consistent – existing reports could already be used ***in lieu of*** a separate national review.

The Pilot Project was equally optimistic about the future prospects for greater co-operation in pesticide review. The project recommended that work begin immediately in five areas to increase the possibility of such co-operation. The work recommended was to:

(1) develop a harmonized data review report structure and content;

(2) create a clearinghouse to list available studies on pesticides;

(3) develop harmonized terminology and criteria for hazard identification;

(4) initiate activities to permit scientific exchange; and

(5) establish mechanisms to organise the immediate exchange of reports.

The Pilot Project urged the OECD to address all five areas straight away so as to seize the opportunity presented by international re-registration of old pesticides, and to maintain the momentum and enthusiasm generated by the discovery that sharing the burden of pesticide review is a realistic and obtainable goal.

Pilot Project Pesticides and Participants

Pesticide	Lead country	Participating countries, organisations
Amitraz	Germany	Canada, Food and Agriculture Organization (FAO), United States
Diazinon	Switzerland	Australia, Canada, Finland, Sweden, United Kingdom, United States
Dicofol	Denmark	FAO, Germany, Netherlands, United States, World Health Organisation (WHO)
Dinocap	Sweden	Australia, FAO, Switzerland, United Kingdom, United States, WHO
Endosulfan	United States	Australia, Canada, Denmark, FAO, Germany, Sweden
Iprodione	Finland	Australia, Canada, United Kingdom, United States, WHO
Pyridate	Netherlands	Australia, Canada, Germany, Switzerland, United States

Résumé

Le présent rapport contient les conclusions et les recommandations du Projet Pilote de l'OCDE pour comparer les analyses des pesticides. Le Projet Pilote a été lancé à la demande des pays Membres de l'OCDE qui ont vu à la fois le besoin et l'occasion d'intensifier la coopération internationale en matière de renouvellement des homologations des anciens pesticides. Le Projet Pilote visait à déterminer comment les pays pouvaient ***se répartir la charge de l'analyse des données sur les pesticides*** en utilisant réciproquement les rapports d'analyse des données plutôt que d'évaluer séparément les mêmes pesticides.

Le Projet Pilote a débuté par l'examen des rapports d'analyse des données existants pour un groupe choisi de pesticides afin de comparer comment différents pays et organisations internationales avaient évalué des données identiques ou similaires concernant les effets sur la santé et sur l'environnement. Le projet a ensuite envisagé dans quelle mesure les rapports existants pouvaient d'ores et déjà être utilisés pour compléter ou remplacer les analyses nationales individuelles. Enfin, le projet a émis des recommandations pour intensifier, dans le futur, l'échange et l'utilisation des rapports entre les pays de l'OCDE.

Le Projet Pilote s'est intéressé à sept pesticides, connus pour avoir été analysés par de nombreux pays et/ou organisations internationales. Les pesticides concernés étaient l'amitraz, le diazinon, le dicofol, le dinocap, l'endosulfan, l'iprodione et le pyridate. Pour chacun de ces pesticides, le projet a comparé les analyses des pays dans les domaines de la toxicologie, de l'écotoxicologie, du devenir dans l'environnement, et, de manière moins détaillée, des propriétés physico-chimiques. Le projet a considéré exclusivement les ***rapports*** d'analyse des données, et non les ***données*** originales sur les pesticides, afin d'éviter toute infraction aux droits industriels quant à la confidentialité des informations commerciales.

Les principaux travaux du Projet Pilote ont été menés par sept pays Membres de l'OCDE qui se sont portés volontaires pour étudier et comparer les rapports d'analyse des données disponibles sur les sept pesticides concernés. Trois autres pays et deux organisations internationales ont également participé au projet en soumettant pour étude les rapports d'analyse des données et en commentant les projets des documents écrits par les pays pilotes. Le tableau ci-après présente les pays pilotes et les participants pour chacun des pesticides du Projet.

La principale conclusion du Projet Pilote a été que l'utilisation réciproque des rapports d'analyse des données sur les pesticides entre les pays membres de l'OCDE et la coopération en matière de renouvellement des homologations, pouvaient commencer immédiatement. Malgré des différences importantes entre les rapports, le projet a conclu que nombre d'entre eux pouvaient utilement ***compléter*** les analyses d'autres pays. De plus, le projet a estimé que dans certains cas – quand les résultats des études sont clairs et les analyses consistantes – les rapports existants pouvaient déjà être utilisés ***à la place*** des analyses nationales individuelles.

Le Projet Pilote était également optimiste quant aux perspectives futures d'une plus grande coopération en matière d'analyse des pesticides. Le projet a recommandé de commencer à travailler immédiatement dans cinq domaines pour accroître la possibilité d'une telle coopération. Il a été recommandé de :

(1) développer une structure et un contenu harmonisés pour les rapports d'analyse des données ;

(2) créer un centre de coordination pour recenser les études disponibles sur les pesticides ;

(3) harmoniser la terminologie et les critères pour identifier les dangers ;

(4) entreprendre des activités pour permettre un échange scientifique ; et

(5) mettre en place des mécanismes pour organiser l'échange immédiat des rapports d'analyse.

Le Projet Pilote a vivement encouragé l'OCDE à examiner de suite les cinq domaines cités afin de saisir l'occasion présentée par le renouvellement international des homologations des anciens pesticides, et afin de maintenir le dynamisme et l'enthousiasme suscités par la découverte du fait que le partage de la charge de l'analyse des pesticides était un objectif réaliste et accessible.

Les Pesticides et les participants du Projet Pilote

Pesticide	**Pays pilote**	**Pays, organisations**
Amitraz	Allemagne	Canada, Etats-Unis, Food and Agriculture Organisation (FAO)
Diazinon	Suisse	Australie, Canada, Etats-Unis, Finlande, Royaume-Uni, Suède
Dicofol	Danemark	Allemagne, Etats-Unis, FAO, Organisation mondiale de la Santé (OMS), Pays-Bas
Dinocap	Suède	Australie, Etats-Unis, FAO, OMS, Royaume-Uni, Suisse
Endosulfan	Etats-Unis	Allemagne, Australie, Canada, Danemark, FAO, Suède
Iprodione	Finlande	Australie, Canada, Etats-Unis, OMS, Royaume-Uni
Pyridate	Pays-Bas	Allemagne, Australie, Canada, Etats-Unis, Suisse

Introduction

This report presents the findings and recommendations of the OECD "Pilot Project" to Compare Pesticide Data Reviews. The Pilot Project was initiated at the request of OECD Member countries during a re-registration workshop in Washington, D.C. in October 1992. At this workshop Member countries agreed that there was both a need and an opportunity to increase international co-operation in the re-registration of old pesticides. The purpose of the Pilot Project was to determine the extent to which countries might ***share the burden of pesticide data review*** by using each other's data review reports, rather than separately evaluating the same pesticides.

The Pilot Project began by examining existing data review reports on a select group of pesticides in order to compare how different countries and international organisations had evaluated the same or similar data on health and environmental effects. The project compared all key aspects of the reports: their structure, content and degree of transparency; the original data sets reviewed; the endpoints assessed; the specific hazard levels identified; and the final hazard characterization of the pesticide. Based on this comparison, the project considered the extent to which existing data review reports might already be used to complement or replace a separate national review. The project also recommended ways to increase the exchange and use of reports among OECD countries in the future.

Scope

Seven pesticides that were known to have been reviewed by multiple countries and/or international organisations, and therefore provided the opportunity for comparison of data review reports, were selected for the Pilot Project.

These pesticides were: ***amitraz, diazinon, dicofol, dinocap, endosulfan, iprodione***, and ***pyridate***.

For each of these pesticides, the project compared countries' reviews in the test areas of toxicology, ecotoxicology and environmental fate, with a less detailed analysis in the area of physical-chemical properties. The areas of efficacy and exposure were intentionally excluded so as to keep the focus on hazard identification and the assessment of data that would be common to all countries.

Two potential problems were addressed early in the project: First, any confidential business information was removed from the data review reports so as to avoid infringement of industry rights with regard to the original pesticide data. The project was thus designed to ensure that the analysis focused not on the pesticide ***data*** but on the data review ***reports***. Second, certain reports or report summaries were translated into English for purposes of the project, although language differences posed fewer problems than expected.

Participants

The principal work of the Pilot Project was done by seven OECD Member countries who volunteered to take a lead role in collecting, analysing and comparing available data review reports on the seven pesticides. Three other countries and two international organisations also participated in the Pilot Project by submitting their data review reports for analysis and by commenting on draft documents written by the lead countries. The table below shows the lead country and participants for each Pilot Project pesticide.

Pilot Project Pesticides and Participants

Pesticide	Lead country	Participating countries, organisations
Amitraz	Germany	Canada, Food and Agriculture Organization (FAO), United States
Diazinon	Switzerland	Australia, Canada, Finland, Sweden, United Kingdom, United States
Dicofol	Denmark	FAO, Germany, Netherlands, United States, World Health Organization (WHO)
Dinocap	Sweden	Australia, FAO, Switzerland, United Kingdom, United States, WHO
Endosulfan	United States	Australia, Canada, Denmark, FAO, Germany, Sweden
Iprodione	Finland	Australia, Canada, United Kingdom, United States, WHO
Pyridate	Netherlands	Australia, Canada, Germany, Switzerland, United States

The success of the Pilot Project must be attributed to the seven lead countries, who devoted a tremendous amount of time and energy to the project. The outstanding work done by these countries can be seen in the "Phase 3" reports attached in Annexes 1-7, which present the results of their individual analyses. The Phase 3 reports, so-called because they were done during the third and final phase of the project, contain the detailed findings of the Pilot Project. These reports, along with the ideas and information discussed at several lead country meetings held during the course of the project, served as the basis for this summary report.

Approach

The Pilot Project was carried out in three phases:

Phase 1 In Phase 1 (March-May 1993) lead countries collected available data review reports on their respective pesticides from the participating countries and international organisations.

Phase 2 In Phase 2 (June-October 1993) lead countries completed a preliminary analysis of the reports by (1) identifying the studies reviewed by each country or organisation, (2) determining the extent to which countries and organisations had reviewed the same studies, and (3) describing the different reports in terms of structure and content. The lead countries also identified specific studies and study categories within the test areas of toxicology, ecotoxicology and environmental fate that would be covered in their final analysis (these areas are identified at the beginning of each Phase 3 report).

This phase also included a survey, conducted by the OECD Secretariat, of the data review process in each country and international organisation participating in the project. This survey was done to support the principal work of the Pilot Project, by providing lead countries with a general idea of the staff and process used to produce the reports they were analysing. The report of this survey is attached in Annex 8.

Phase 3 In Phase 3 (November-May 1994) lead countries completed their analysis and comparison of the data review reports by examining the extent to which they:

- followed a format that was clear and easy to read;
- cited clearly the original studies reviewed;
- documented, or described, those studies in adequate detail;
- evaluated the same studies;
- reported the same endpoints;
- identified the same hazard level; and
- reached the same overall conclusion about the pesticide.

Based on this analysis, Phase 3 identified key areas where work needed to be done to make countries' reports more easily useable by others.

Findings and Recommendations

The central finding of the Pilot Project was that mutual use of pesticide data review reports among OECD Member counties, and co-operation in re-registration, could begin straightaway. Despite the considerable differences among existing data review reports, the Pilot Project found that many could usefully complement another country's independent review. Moreover, the project found that in certain areas – where study results are straightforward and countries' analyses consistent – existing reports could already be used in lieu of a separate national review.

The Pilot Project was equally optimistic about the future prospects for greater co-operation in pesticide review and mutual use of data review reports. While several barriers to such co-operation were identified, the project concluded that none of these barriers was insurmountable. The project thus recommended that work begin immediately in five main areas:

(1) report structure and content;

(2) studies reviewed;

(3) terminology and criteria for hazard identification;

(4) the data review process; and

(5) exchange of reports.

Report Structure and Content

The first step recommended by the Pilot Project was to develop a harmonized structure and content for pesticide data review reports written by OECD countries. The purpose would be to ensure that reports were clearly organised, easy to read, and contained all information that might be needed by another country.

The reports examined in the Pilot Project represented a wide variety of document types and styles. They included long, detailed documents and short, summary reviews; reports that were organised by test area (i.e. covering all studies done in one area) and others that focused on individual studies. These differences made the reports difficult to compare and, in some cases, to read. But most important was that, in many of the reports, key information was lacking or unclear.

The project concluded that one of the quickest steps to report sharing and use would be the adoption of a harmonized report structure and format that included the following components:

(i) a clear and well-ordered structure with consistent treatment of studies and inclusion of document signposts such as headings, tables of contents, introductions and conclusions, and summary evaluations at the end of study sections to pull the information together;

(ii) a standard format for bibliographies and data citation that specifies whether studies are to be listed by laboratory or author, whether dates refer to completion of the study or publication of the study report, etc.; and

(iii) sufficient detail to make the report fully transparent with regard to (1) ***the studies reviewed***, their compliance with principles of good laboratory practice, test guidelines and other quality control criteria, and their acceptance or rejection in the country's evaluation of the pesticide; and (2) the ***thought process and decision logic*** of the reviewer, i.e. how he interpreted specific study results and judged their importance, and how he arrived at his final conclusion about the pesticide.

Studies Reviewed

The second step recommended by the Pilot Project was to develop a central OECD clearinghouse to list, and possibly describe, all studies done on relevant pesticides. The purpose would be two-fold: (1) to inform countries about all data available on pesticides undergoing registration or re-registration, and (2) to avoid unnecessary testing by industry.

The Pilot Project found that OECD countries had often reviewed different data in their assessment of the same pesticides, despite their common purpose of determining possible health and environmental effects. Two possible reasons for these differences are:

(i) the date of study completion and submission to a regulatory authority (new studies would only have been reviewed in recent reports); and

(ii) different national registration requirements, such as data requirements and test guidelines.

The project also found that short-term tests, such as acute toxicity and ecotoxicity studies, were more likely to be repeated than longer tests such as cancer and reproductive and developmental effects studies.

The Pilot Project recommended consideration of two different approaches to a clearinghouse that would support countries' data review and (re)registration programmes:

(i) a simple bibliography of all studies done on the pesticides; and

(ii) an annotated bibliography of the studies with information on study findings, dates of review and (re)registration by OECD countries, and general outcome of countries' reviews.

Terminology and Criteria for Hazard Identification

The third step recommended by the Pilot Project was to develop harmonized terminology and criteria for hazard identification. While this is already a recognized goal of the OECD and other organisations, the Pilot Project demonstrated both the need for greater harmonization and reasons why it should be achievable. Most important, the project found that countries generally agreed in their overall assessments of the pesticides. In almost all cases, they:

- focused on the same endpoints as being important; and
- came to the same overall conclusion about a pesticide's hazard – agreeing on the key hazards posed and the general degree of concern – even when they had reviewed different studies or reported different hazard levels such as No Observable Effect Levels (NOELs) for specific endpoints.

On the other hand, the project found important differences in countries' reporting and assessment of the results of individual studies. These included using different terms to describe the same effect, reporting different NOELs or other hazard levels (even when reviewing the same studies), and judging differently the meaning or importance of certain effects.

Inconsistency in terminology was found in all study areas, but was particularly prevalent for reproductive and developmental toxicity. Countries used a variety of terms – teratogenicity, embryotoxicity, fetotoxicity, and embryofetotoxicity – to describe the same developmental effect. Similarly, the term "reproductive toxicity" was varyingly used to refer to the general test area, to effects on adults, or to effects seen in one-, two- or multi-generation studies. Inconsistency in terminology was also important in the study area of carcinogenicity, where it was linked to the use of different diagnostic criteria.

Different hazard levels were also reported in multiple test areas. For example, countries reported different:

(i) LD_{50}s on dicofol depending on whether they report an LD_{50} as an exact value (e.g. 1495 mg/kg bdw) or an interval (e.g. 500-5000 mg/kg bdw);

(ii) half lives, or DT_{50}s, for soil degradation of pyridate depending on use of an exact value (e.g. 35 days) or range (e.g. 10-60 days); and

(iii) levels of irritation and/or sensitization for the pesticides dicofol, amitraz and pyridate, perhaps resulting from use of different hazard classification schemes.

Differing judgments about the importance or meaning of an effect were similarly seen in various areas. For example:

(i) Countries set widely different NOELs for iprodione depending on whether they took into account unpalatability of the diet as a factor in reduced weight gain, whether they considered hyper-reflection to be a toxic effect, and the importance they assigned to an anaemic tendency and to reduced dam and litter weights; and

(ii) Countries assigned varying cancer classifications to amitraz depending on the biological significance given to increased tumours in liver, lung and lymphoreticular systems, and on the terminology and criteria used to diagnose neoplastic and non-neoplastic lesions.

Acknowledging that resolution of these inconsistencies was key to international co-operation, but also that various national and international activities were already under way to do just that, the Pilot Project recommended that:

(i) information on existing activities be consolidated and presented to OECD countries; and

(ii) this list of activities be compared with the Pilot Project findings, in order to see where additional work should be initiated or greater priority placed. Areas highlighted by the Pilot Project as most in need of harmonization included:

- schemes for hazard classification;
- approaches to hazard evaluation, such as methods for setting a NOEL and for evaluating other endpoints for both ecological and human toxicity;
- terminology and criteria for interpreting studies in the areas of chronic toxicity and carcinogenicity, reproductive and developmental toxicity, metabolism, and toxicokinetics (within these general areas, the project identified a specific need for guidance on use of historical controls, on statistical procedures such as use of mean measured vs. nominal concentrations, and on determining biological and statistical significance);
- models for predicting environmental concentration; and
- endpoints to assess worker exposure, as well as standards for human epidemiological studies (nb: although these two areas were not covered in the Pilot Project, the data review reports which included them showed a wide variation in national approaches).

The Data Review Process

The fourth step recommended by the Pilot Project was to initiate activities to permit scientists from different countries to work together so as to become familiar with each other's approaches to pesticide data review. The purpose would be to increase countries' level of comfort with each other's work, thereby paving the way for increased exchange and use of data review reports in the future.

Such activities could include:

- short-term staff exchanges to allow scientists to work with foreign colleagues and to understand, first-hand, the functioning of other systems;
- conduct of ring (or round-robin) assessments to allow scientists to compare their data reviews with those of foreign colleagues; and
- periodic updating of information on the pesticide review processes and re-registration programmes in OECD countries (based on the Pilot Project survey of participating countries and organisations attached in Annex 8).

Exchange of Reviews

The fifth recommendation of the Pilot Project was to establish mechanisms whereby countries could begin straightaway to exchange and use each other's pesticide data review reports to complement their own registration and re-registration efforts. The project concluded that such an exchange should begin immediately, to take advantage of the momentum created by the Pilot Project as well as the opportunity presented by the international re-registration of old pesticides.

Immediate action

In certain study categories, existing reports could be used without a re-review of the original data. For example, in the areas of:

- acute oral and dermal toxicity (mammals);
- acute ecotoxicity (fish, birds, invertebrates); and
- environmental fate (laboratory studies)

the Pilot Project showed almost complete agreement in countries' interpretations of study results (a finding that was not surprising because the studies leave little margin for interpretation).

Reports could also possibly be used without re-review in two other areas where study results are straightforward, even though countries' conclusions were not always consistent. These include:

- acute inhalation studies (current differences in interpretation of study results could be resolved through consistent use of OECD Test Guidelines); and

- dermal and eye irritation studies (harmonization of terminology would enable countries to use others' interpretation of study results).

Long-term activities

In the more complex study areas, where use of reports without re-review is less likely, the Pilot Project recommended that OECD establish work groups of two to three countries to address key issues and differences. These work groups would need to take account of, and contribute to, other ongoing projects to harmonize hazard identification approaches (including those initiated as a result of the Pilot Project). Study areas to be addressed could include, for example:

- chronic toxicity and carcinogenicity;

- reproductive and developmental toxicity;

- chronic ecotoxicity; and

- environmental field testing.

Conclusion

The key finding of the Pilot Project was that OECD co-operation in pesticide review and re-registration could and should begin immediately, with mutual sharing and use of data review reports to complement separate national reviews. Such co-operation could occur with existing data review reports, despite their many differences and inconsistencies.

The Pilot Project recommended work in five areas to increase the degree to which countries could use each other's reports and co-operate in pesticide review in the future. The work recommended was to:

(i) develop a harmonized data review report structure and content;

(ii) create a clearinghouse to list available studies on pesticides;

(iii) develop harmonized terminology and criteria for hazard identification;

(iv) initiate activities to permit scientific exchange; and

(v) establish mechanisms to organise the immediate exchange of reports.

The Pilot Project urged the OECD to address all five areas straightaway so as to seize the opportunity presented by international re-registration of old pesticides and to maintain the momentum and enthusiasm generated by the project's discovery that sharing the burden of pesticide review was a realistic and obtainable goal.

ANNEX 1

PHASE 3 REPORT

ON

AMITRAZ

Lead Country: Germany

Contents

Introduction

For the purposes of this project, evaluations of amitraz were submitted by the following countries and organisations:

- Canada
- Germany
- United States
- Food and Agriculture Organization (FAO)

Although Switzerland indicated participation as well, legal restrictions prevented the Swiss authorities from delivering any evaluation or bibliography.

Unfortunately, the disciplines **product chemistry, fate and behaviour in the environment, and ecotoxicology** were only covered by the reviews of the United States and Germany (the FAO reviews list product chemistry data but not the studies). Thus, the comparison in these disciplines was limited to only two evaluations. As for the discipline **toxicology and metabolism**, four evaluations (Canada, Germany, United States, FAO) were available, making the situation here rather different from the other disciplines.

Further, reflecting the burden-sharing among German agencies, the German evaluation of amitraz consists in fact of two rather different parts, one of them covering toxicology and metabolism (compiled by the Federal Health Agency BGA), the other covering all other disciplines (compiled by the Federal Biological Research Centre for Agriculture and Forestry BBA). Therefore, it seemed advisable to split this report into two parts, one of them covering **environmental fate and ecotoxicology (Part 1)**, the other dealing with **toxicology and metabolism (Part 2)**.

In phase 2 of the Pilot Project, study identification tables for each test area were completed. If the endpoint could be identified from the title or the review, this study was listed in the bibliography. Studies where the endpoint was not identifiable were not listed.

Based on these tables, special study categories were selected for the in-depth analysis of phase 3. As agreed among the OECD Secretariat and the seven lead countries, **product chemistry** was excluded from further analysis. For amitraz, phase 3 focuses on the following areas:

Part 1: Environmental fate and ecotoxicology

Fate and behaviour in the environment

- hydrolysis rate including identification of metabolites and breakdown products
- photodegradation in water including identification of metabolites and breakdown products
- soil metabolism, aerobic and anaerobic, in representative soil types
- mobility/leaching in representative soil types and mobility of metabolites and breakdown products
- adsorption/desorption in representative soil types including metabolites and breakdown products

- extent and nature of bound residues in soil
- field dissipation (additionally included because of its importance)

Ecotoxicology

- avian acute oral LD_{50}
- avian dietary toxicity LC_{50} - terrestrial bird (short-term)
- avian dietary toxicity LC_{50} - aquatic bird (short-term)
- avian reproduction test - terrestrial bird

- fish acute toxicity LC_{50}, freshwater, warm-water species
- fish acute toxicity LC_{50}, freshwater, cold-water species
- Daphnia acute immobilization test
- Daphnia life-cycle
- chronic toxicity to fish or fish early life stage

- acute toxicity to honey bees LD_{50}
- earthworm, acute toxicity test
- algae, growth inhibition

Part 2: Toxicology and metabolism

- acute toxicity
- subchronic toxicity (species sensitivity)
- developmental and reproductive toxicity
- chronic toxicity (species sensitivity, carcinogenicity)
- neurotoxicity testing.

PART 1: ENVIRONMENTAL FATE AND ECOTOXICOLOGY

1.1 Types of data reviews

The data reviews in these test areas were rather different in style, length and content even within the evaluation of one country. Therefore, the reviews for environmental fate and for the different areas of ecotoxicology are discussed separately. Aspects common to all reviews of one country can be found in the discussion on fate (para 1.1.1). For detailed information on whether the review of a certain study provides information on the test guideline, GLP or acceptability, see Table 2 (Appendix 1).

Both countries submitted their "normal" dossier, with three adjustments in the German dossier necessary for participation in this project: the dossier was translated into English, references and a bibliography were included, and test results with formulations were removed if data on the active ingredient were available.

The German review is one document of altogether 28 pages including the bibliography (except toxicology). Two pages provide key information on identity, physical chemistry data, manufacturer and stability. Some chapters were deleted due to the legal restrictions and to their not being part of the evaluation in the context of the Pilot Project (efficacy and use, residue trials, pre-harvest intervals, maximum residue levels, analytical methods). Thus, it can be concluded that Germany uses a fixed structure for these reviews. Their structure indicates that they summarize all the available key information (necessary for the decision making process) in one document.

The review of the US consists of many individual and rather different reviews, ranging from Data Evaluation Records (most of them < 10 pages, but up to 30 pages, e.g. for subchronic fish tests; covering one study in great detail) to more aggregated reviews (from 2 to approximately 30 pages) covering several studies. Some of these "higher tier reviews" offer risk assessments on certain aspects. There is no up-to-date summary on all of these reviews. All reviews together have several hundred pages (the pile is about 12 cm high; most of it double-sided). Unfortunately, most of the reviews are attached to letters to/from EPA, the applicant, contractors or other EPA branches. Thus, the reader from outside EPA who is only interested in certain properties of amitraz has difficulties finding the piece of information. From the cover sheet of the documents, it is often difficult to tell what kind of data (aggregated review, data evaluation records or letters to/from companies and other EPA branches) is included. To be sure that a certain piece of information is not available, one has to read all the aggregated reviews.

Often, several reviews of different age deal with the same test area but the status of the older ones is not clear (e.g. overruled by the newer review?). The aggregated reviews seem to have been compiled:

- either to respond to the intended extension of registered uses, referring often to the situation in these "new" crops,

- or to evaluate several supplementary studies which were submitted as a response to data requests,

- or to respond to supplementary studies or information which were submitted as a response to a waiver request.

From the reviews concerning the amendment of registered uses it becomes clear that data requirements are not the same for all outdoor applications but depend on the crop.

For more detail, see the following discussion of the different test areas.

1.1.1 Fate in soil and water

The German review on fate is short (3 pages) and highly aggregated thus being a summary of the available information. The compartments soil, water and air are discussed. Key findings from the evaluated studies are summarized in both text and tables. Depending on the number of studies evaluated for a certain endpoint, either one value or a range is presented. The discussion is focused on the endpoints, not on individual studies. Thus, if there are several studies used for the evaluation of the same endpoint, they are discussed in context, not separately. Except test duration and sampling dates, methods or details on study design, test guideline, GLP or other validity criteria are not reported. Conclusions on the facts/results are given, but details on uses, use restrictions or other regulatory decisions are not included.

The US reviews on fate range from individual Data Evaluation Records to more aggregated reviews like the Environmental Fate and Ground Water Branch Reviews (> 30 pages). Many of the reviews were prepared by contractors from outside EPA. Data Evaluation Records give details on test design, results and reviewer's conclusion about acceptability and (sometimes) GLP. However, they do not mention the specific test guideline. This information can only be found in the attached memoranda, accompanying letters or EFGWB reviews.

The more aggregated reviews still discuss each study in more detail than the German review and offer comments on whether or not the test requirements for certain uses are fulfilled. Further, these reviews point out where studies lack certain essential details, where requirements are not met or where there are doubts on certain findings. Recommendations on further action by EPA are given. Reasons for further requirements or for rejection of studies are also included. However, there is no single document which could be regarded as **the** up-to-date environmental fate review, reporting all the available information.

In comparison, both countries use the same or a very similar data base. Both evaluate not only studies with amitraz but also with formulations and metabolites. It cannot be identified whether the formulation (a 20% EC) is identical. The US evaluates additional data about photodegradation on soil whereas Germany evaluates additional data about the fate in water/sediment systems. There are no obvious terminology or measurement differences.

1.1.2 Ecotoxicology

Avian testing

The German review is short (1 page) and presents the key findings of the evaluated studies on acute toxicity (oral), sub-acute toxicity (oral) and reproduction. A tabular summary is not included. An overall risk assessment for the use in hops is included. Use restrictions or other regulatory decisions are not reported. Everything else is as described for the review on environmental fate.

The US reviews on avian testing consist of individual Data Evaluation Records (< 10 pages, covering one study in detail), some of them bound together and briefly (< 5 pages) summarized (partially in tables) in attached Ecological Effects Branch Reviews. Overall risk assessments are provided in two of the reviews prepared in response to the amendment of uses. As in fate, there is no single document covering all the available studies. More reviews than in the fate part comment on GLP. Everything else is as described for the review on environmental fate.

In comparison, the US required acute and dietary studies for two metabolites that were not required by Germany. The US rejected three reproduction studies that were obviously accepted by Germany. In the overall conclusion the US rated the risk to terrestrial wildlife slightly higher than Germany (the assessment of the US was stated to be preliminary).

Aquatic testing

The German review is short (3 pages) and presents the key values of the evaluated studies in tabular format. Although the bibliography lists studies with a formulation, these data are not included. An overall risk assessment for the use in hops and viticulture is included in terms of predicted environmental concentrations, an environmentally relevant concentration (the tolerable concentration in surface waters), labellings and use restrictions (buffer zones to surface waters). Everything else is as described for the review on environmental fate.

The US reviews on aquatic testing are comparable to the ones for avian testing. The overall risk assessment, risk phrases and use restrictions are given in the same two reviews prepared in response to the amendment of uses. As in fate, there is no one document covering all the studies. More reviews than in the fate part comment on GLP. Everything else is as described for the review on environmental fate.

In comparison, the data bases evaluated by the two countries were very similar. The US used toxicity data of the formulated product for the characterization of the active ingredient, whereas Germany, due its legal restrictions, listed only the data on the active ingredient in the dossier. The unit of measure for concentrations in some of the US reviews is ppm, in other reviews mg/l.

Other non-target species (earthworms)

Germany provides a tabular summary of the few available data. There are no comments on risk assessment, labellings etc. It is mentioned that the available test was **not** done according to OECD 207, but the method or guideline which was actually used is not mentioned.

The US reviews do not mention studies or results for earthworms.

Phytotoxicity to non-target plants; algae, growth inhibition

As to the German review, this test area is part of the aquatic testing (see above for discussion). The US reviews do not mention studies or results with algae.

1.2 Comparison of values/results reported in the data reviews

Table 1 (attached) lists the study reference, study type, test substance endpoint(s) and values reported by each country. It also states for each country if the study was not reviewed (**-**) or whether the information is missing (*****). The study reference is coded for the test area by one or two capital letters, followed by a capital or small letter indicating the individual study within each test area (sorted by endpoints).

1.2.1 Identity of the data base

For physical-chemical properties, environmental fate and ecotoxicology, an analysis of the report done for phase 2 of the Pilot Project shows that of a total of 122 studies referenced in the review report bibliographies, roughly one third were either cited in the report texts by both the US and Germany or by only one of the two countries. Twenty-two studies (18%) could not be assigned to a specific endpoint, most of them dealing with physical-chemical properties and beneficial arthropods.

For the 78 study citations (due to multiple use of some studies on environmental fate, the actual number or studies is smaller) selected for phase 3, the degree of overlap (i.e. studies used by both countries) is higher (42%). This is mainly due to the 49% overlap in ecotoxicology whereas for environmental fate the distribution is still one third in each category. Table 3 provides a detailed breakdown of the frequency of the study citation.

1.2.2 Comparison for fate in soil and water

As previously stated, the US reviews always include a description of methods including any deviation from the test guideline. The endpoints are generally very similar, with the US often evaluating mass balance and providing more detail on metabolites. For degradation in soil, Germany also evaluates DT_{90} values while this seems not to be necessary for the US evaluation. The common and different endpoints are listed below in more detail.

If not stated otherwise (only two cases), there are no differences in evaluating the same study for the same endpoint.

Hydrolysis

- half-lives of amitraz and its degradates at different pH
- degradation products.

US reviews include more details (amount) on degradation products and provide mass balances.

Photodegradation in water

- half-lives under certain Ph-values and artificial light and natural sunlight
- nature (the US also gives amounts) of main metabolites.

For one study (F-F), both countries report different half-life values (11.8 h to 26.4 days). From the US review it became clear that Germany reported the half-life after adjustment of the data for the dark control (46.5 h) while the conclusions of the US review list the unadjusted half-life (11.8 h). The "environmental half-life" values reported by both countries (Germany 3.3-4 d for central Europe; US 3.27-26.4 d) were calculated using intensity simulation programmes for different seasons and the geographical zone of concern. Thus, there is no difference in the evaluation of this study. However, it is not clear from the US review why the conclusions only list the unadjusted half-life and whether this value is really used for further assessments.

Soil metabolism and degradation

- DT_{50} (Germany also gives DT_{90}) values of amitraz and metabolites under aerobic laboratory and field conditions in different soils
- metabolic pathway
- amounts of main metabolites, extractable and bound residues.

Mobility/leaching

- leaching of amitraz and main degradates
- amounts in leachates and top soil (also in different soil layers for the US)
- further degradation of amitraz during leaching
- results of aged leaching experiments.

US reviews also include mobility classification and mass balances.

Adsorption/desorption in soil

- K_{OC} in different soils.

Germany also uses K_d while US uses K_f, log K_{OW} and pK_a plus amounts of major and minor degradates.

Bound residues

Germany evaluates with some flexibility the nature and extent of bound residues at different times while the EPA uses more rigidly fixed endpoints (extent of bound residues after 364 d under aerobic and after 60 d under anaerobic conditions).

Field dissipation

Germany evaluates a DT_{50} for the sum of degradates in field soil and the total residues after one year. The US reviews are more specific (DT_{50} of amitraz and its degradates, concentrations in different soil depth at different times). For one study (F-M) Germany does not report the DT_{50} for the active ingredient (US: << 1 d), obviously because this value is of no importance for the assessment compared to the far more stable major metabolites (DT_{50} 110 and 150 d, respectively). Thus, the key finding of the study is the same for both countries.

1.2.3 Comparison for ecotoxicology

As for the fate reviews, the US reviews on ecotoxicology testing include detailed description of methods including any deviations from the test guideline. Further, comments on statistical evaluation of the test results or the calculations are reported. The reviews also include a summary of the results including LD_{50} and NOED (avian acute oral), LC_{50} and NOEC (avian short-term dietary; aquatic testing) plus observations on clinical/behavioural signs of toxicity. However, these observations on any effects at levels above the NOEC/NOED get more attention with longer-term tests.

Nominal dose or concentration levels and any deviations from these levels are generally reviewed by the US while Germany reports this information only for sub-chronic tests. Both countries report test species and, with the avian tests, the age.

With the **avian tests**, there are no differences when the same study was evaluated. For the study type "reproduction toxicity: one-generation mallard duck", however, the countries report different NOEC-values (from different studies) ranging from 24.6 ppm to 100 ppm. As both countries use embryo mortality as one of the endpoints determining the NOEC, the source of the different evaluation is unclear.

With the **aquatic tests**, Germany's review includes considerably more information on the longer-term tests (such as behavioural symptoms, test system like flow-through or semi-static, concentration levels both nominal and measured, solvents and radioactive labelling) than on the acute tests.

A few differences with evaluations of the same study can be observed. For the acute toxicity study EF-B, the US conclusions for NOEC and LC_{50} are based on mean measured concentrations, while Germany lists the results based on the nominal concentrations that are reported by the US. For the studies EF-F and EF-b, the differences are due to different statistical procedures for calculating the LC_{50}. Germany used the method proposed by the study author (angle transformation and linear interpolation) while the US reviewer re-calculated the LC_{50} with EPA's Toxanal computer programme. For study EF-E, Germany's conclusion on the NOEC is based on mortality whereas the US observed effects (behavioural?) at every test level, thus setting the NOEC below the lowest test concentrations.

The German review of **earthworm acute toxicity** lists species, test duration, LC_{50}, LOEC, and NOEC. Earthworm tests were not covered by the US review.

1.2.4 Gaps and conclusions

In general, it can be stated that there are remarkably few differences in the evaluation of amitraz. Most endpoints used are identical, with slightly different attention being paid to the extent of some details (see above). In those study types which were selected for phase III, the data base reflecting the requirements are very similar. The major differences here are:

- more soil metabolism studies in the German review
- far more avian studies (species) in the US review
- algae growth inhibition study only in the German review
- earthworm toxicity only in the German review.

However, it should be noted that there are more differences with those study types that were not selected (in brackets the country whose review includes these data):

- fate in water/sediment systems (Germany)
- photodegradation on soil (US)
- distribution/dissipation in air (Germany)
- marine/estuarine fish toxicity (US)
- marine/estuarine invertebrate toxicity (US)
- beneficial arthropods (Germany).

As far as can be derived from the reviews, the overall conclusions of the two countries about the hazard of amitraz are also very similar. There may be differences in the assessment of specific uses and in use restrictions, but as stated above, specific uses are only occasionally included in both reviews.

One important point is the use of test guidelines. The German review hardly mentions specific guidelines but when studying the German guidance for applicants it becomes clear that in many test areas OECD guidelines are used. As can be seen in Table 2, US EPA guidelines are accepted frequently. With the US, the only guidelines mentioned specifically are EPA guidelines. There are not many studies where this kind of information is missing in the US reviews.

1.3 Potential for use of other countries' reviews

The use of other countries' reviews will be introduced for all member states of the EU by the implementation of the European Community's system for registration and re-registration of plant protection products. Details on how such reviews have to be structured and to what extent data have to be reported are still under discussion. So far, there is no experience with using other reviews for regulatory decisions. Thus, this report can only give indications of what would be necessary for such reviews.

The assessment in many test areas is not based on a single value. The risk-benefit analysis for the overall decision also takes into account factors like the slope of the dose-response relationship, number of applications per year, etc. Thus, for most cases, at least tables of the raw data would be necessary. The level of documentation used in the Data Evaluation Records of US EPA could in many cases allow them to be evaluated instead of the original study. The discussion of why a certain study has been rejected is very useful. Thus, the structure of these study reviews could be a start. However, the higher aggregated reviews would need a much clearer system. In their current structure they could not be used mainly due to their being prepared for separate numbers of original studies and for different purposes. Sometimes, neither the Data Evaluation Records nor the aggregated reviews could be used because the important endpoint is missing (DT_{90} in environmental fate). At any rate, access to the original study report would be necessary in important cases.

1.4 Recommendations

The mutual use of reviews, bibliographies and assessments could be greatly encouraged by agreement on the following items:

- standard structure of study citation in order to allow easy comparison of bibliographies
- standard structure for reviewing individual studies
- standard structure for aggregated reviews for whole test areas
- guidance on statistical procedures
- use of mean measured versus nominal concentrations
- legal agreement on what type of data (raw versus aggregated; existence of studies etc.) is free to share among government agencies and other bodies
- agreement on test guidelines.

Appendices on environmental fate and ecotoxicology

Appendix 1. Tables

Table 1. Endpoints and Results

Ref.	Study type	Endpoint		Value/Result	
				D	US
FATE AND BEHAVIOUR IN THE ENVIRONMENT					
Hydrolysis					
F-A	Hydrolysis	AI	half-life	Ph 4.99: 0.97h Ph 7.05: 15.5 h Ph 9.20: 32.0 h	-
F-B	Hydrolysis	AI	half-life	Ph 5: 2.1 h Ph 7: 22.1 h Ph 9: 25.5 h	Ph 5: 2.1 h Ph 7: 22.1 h Ph 9: 25.5 h
F-C	Hydrolysis	M	half-life	pH 5: 2801 d pH 7: 14 d pH 9: 5.1 h	pH 5: 2800 d pH 7: 14 d pH 9: 5 h
F-D	Hydrolysis	M	half-life	pH 5: 2280 d pH 7: 14500 d pH 9: 496 d	pH 5: 2280 d pH 7: 14500 d pH 9: 496 d
F-E	Hydrolysis	FM	half-life metabolism	-	see F-B, F-C, F-D
Photodegradation in water					
F-F	Photolysis	AI	half-life environmental half-life	46.5 h 3.3-4 d central Europe	11.8 h 3.27-26.4 d
F-G	Photolysis	AI	half-life	4 d	4 d
F-E	Photolysis	FM	*	-	*
Soil metabolism, aerob/anaerob					
F-E	Soil metabolism, aerob	M M M M FM	DT_{50} BTS 27271 (lab) DT_{50} BTS 27919 (lab) DT_{50} BTS 27271 (field) DT_{50} BTS 27919 (field) DT_{50} field	- 	75 d 89 d 50 d 40 d < 1 d
F-K	Soil metabolism	AI M M M	DT_{50} lab DT_{90} lab metabolism and mass balances main metabol. DT_{90} BTS 27271 DT_{90} BTS 27919 DT_{90} BTS 24868	< 1 d 1-6 d aerob; described by examples BTS 27271 BTS 27919 BTS 24868 CO_2 23 d 85 d 51 d	< 1 d aerob; anaerob; described by examples BTS 27271 BTS 27919 BTS 24868 CO_2

				Value/Result	
Ref	**Study Type**	**Endpoint**		**D**	**US**
F-L	Degradation in soil	AI	DT_{50} lab DT_{90} lab	< 1 d 1-6 d	-
F-M	Degradation in soil	AI FM	DT_{50} field for sum of BTS 27271 and BTS 27919	130-150 d	-
F-N F-O	Degradation in soil	AI	DT_{50} lab, extr. total residues DT_{90} lab, extr. total residues	3-13 d 42-88 d	- -
F-V	Degradation and leaching	AI	aged leaching	< 1% in eluat after 45 d	-
F-W	Water/Sediment Micro-cosm	AI M M	DT_{50} microcosm metabolism and mass balances DT_{50} BTS 27271 DT_{50} BTS 27919 (both whole microcosm)	- - - -	3.4-6 h anaerob; described by examples 6.1-7.7 d 10-21 d
Mobility/leaching					
F-E	Mobility/leaching	FM	leaching	-	< 5% unidentified residues in column leachates, degradates should bind to soil.
F-Q	Mobility/leaching	AI	leaching	not eluted	-
F-R	Mobility/leaching	M	leaching BTS 27271	not eluted	< 0.3% of ^{14}C activity eluted
F-S	Mobility/leaching	M	leaching BTS 27919	at most 3.1% eluted	< 3.1% eluted, mobil
F-T	Mobility/leaching	AI	aged leaching	at highest 5% unknown residues in leachate	1.55-5.2% of appl. activity in leachate; not known degradates
F-U F-V	Mobility/leaching	AI	aged leaching	at highest 5% unknown residues in leachate	-
F-Y	Mobility/leaching Adsorption	AI	mobility	-	intermediately mobile in sandy loam, silt loam, clay soils; very mobile in sand

				Value/Result	
Ref	**Study Type**	**Endpoint**		**D**	**US**
Adsorption/desorption					
F-E	Adsorption/desorption in soil	FM	$logK_{OW}$ pKa	-	Amitraz: 5.5 BTS 27271: -0.83 BTS 27919: 1.63 Amitraz: 4.2 BTS 27271: 9.3 BTS 27919: 14.1
F-P	Adsorption/desorption in soil	AI	K_{OC} degradates (> 10%)	364-2000 8 (sand) - 60 (clay)	 8 (sand), 12 (sandy loam) 30 (silt loam) 60 (clay) BTS 27919 BTS 27271 BTS 28037
F-W	Adsorption/desorption in soil	AI	distribution between air, water sediment	-	described by examples
F-X	Adsorption/desorption in soil	AI	Kf	-	15.8-91.7
F-Z?	Adsorption/desorption in soil	AI	*	-	*
Bound residues					
F-K	Degradation in soil	AI	Bound residues after 7-30 d 365 d 60 d anaerob nature of bound residues	 up to 80% 53-65% BTS 27919 BTS 24868	* 52.9-64.5% 72.8-77.5% * *
Field dissipation					
F-M	Field dissipation	AI FM	DT_{50} field, for sum of BTS 27271 and BTS 27919 concentrations in different soil depth	130-150 d	<< 1 d a.i. BTS 27271 110d BTS 27919 150d total 450d described by examples
F-b	Field dissipation	AI	total soil residues (rotational crops)	-	0.07-0.28mg/kg immediately post application 0.6 mg/kg at last harvest, no leaching
F-E	Field dissipation	M M FM	DT_{50} BTS 27271 (field) DT_{50} BTS 27919 (field) DT_{50} field	-	 50 d 40 d < 1 d

				Value/Result	
Ref	**Study Type**	**Endpoint**		**D**	**US**
ECOTOXICOLOGY					
Avian testing					
EB-A	Acute oral, bobwhite	AI	LD_{50}	788 mg/kg	788 mg/kg
EB-K	Acute oral, bobwhite	M	LD_{50}	-	71 mg/kg
EB-C	5-day-dietary, bobwhite	AI	LC_{50}	3081 ppm	3081 ppm
EB-L	5-day-dietary, bobwhite	M	LC_{50}	-	1276 ppm
EB-M	5-day-dietary, bobwhite	M	LC_{50}	-	> 5200 ppm
EB-B	5-day-dietary, Jap. quail	AI	LC_{50}	1800 ppm	1800 ppm
EB-E	5-day-dietary, mallard duck	AI	LC_{50}	7000 ppm	7000 ppm
EB-Q	5-day-dietary, mallard	M	LC_{50}	-	> 5200 ppm
EB-R	5-day-dietary, mallard	M	LC_{50}	-	> 5200 ppm
EB-P	supplement to EB-B	AI	?	-	*
EB-D	supplement to EB-C	AI	Effect. conc.	*	*
EB-N	supplement to EB-L and EB-Q	M	Effect. conc.	-	*
EB-O	supplement to EB-R and EB-M	M	Effect. conc.	-	*
EB-G	One-generation, bobwhite	AI	NOEC	40 ppm	< 40 ppm
EB-H	One-generation, bobwhite	AI	NOEC	40 ppm	40 ppm
EB-X	One-generation, bobwhite	AI	NOEC	-	24.6 ppm
EB-F	One-generation, mallard	AI	NOEC	100 ppm	-
EB-S	One-generation, mallard	AI	NOEC	-	< 40 ppm
EB-Z	One-generation, mallard	AI	NOEC	-	24.6 ppm
EB-I	Supplement to EB-H	AI	Effect. conc.	67-91%	67-91%
Aquatic testing					
Fish					
EF-A	acute, rainbrow trout	AI	LC_{50}	*	2.7-4 ppm
EF-B	acute, bluegill sunfish	AI	LC_{50}	0.45 mg/l	0.34 ppm
EF-B	acute, bluegill sunfish	AI	NOEC	< 0.22 mg/l	0.22 ppm
EF-C	acute, bluegill sunfish	M	LC_{50}	< 6.8 mg/l	< 6.8 ppm
EF-C	acute, bluegill sunfish	M	NOEC	30 mg/l	29.98 ppm
EF-D	acute, bluegill sunfish	M	LC_{50}	> 100 mg/l	> 100 ppm
EF-E	acute, rainbrow trout	M	LC_{50}	27.9 mg/l	28.36 ppm
EF-E	acute, rainbrow trout	M	NOEC	13.4 mg/l	< 4.9 ppm
EF-F	acute, rainbrow trout	M	LC_{50}	74 mg/l	66.23 ppm
EF-F	acute, rainbrow trout	M	NOEC	31.4 mg/l	31.44 ppm
EF-G	acute, rainbrow trout	FM	LC_{50}	*	2.1 mg/l
EF-H	acute, rainbrow trout	FM		-	*
EF-I	acute, rainbrow trout	FM		*	-
EF-K	acute, rainbrow trout	FM		*	-
EF-L	acute, rainbrow trout	FM		*	-
EF-M	acute, rainbrow trout	AI		*	-
EF-O	acute, bluegill sunfish	M, AI		*	-
EF-P	acute, mirrow carp	FM		*	-
EF-Q	acute, rainbow trout	FM		*	-
EF-R	acute, sheepshead minnow	AI	NOEC	-	0.09 mg/l
EF-S	acute, sheepshead minnow	FM	LC_{50}	-	7.94 mg/l
EF-T	acute, sheepshead minnow	FM		-	*
EF-U	acute, sheepshead minnow	M	LC_{50}	-	11.5 mg/l
EF-U	acute, sheepshead minnow	M	NOEC	-	2.36 mg/l
EF-V	acute, sheepshead minnow	M	LC_{50}	-	> 102 mg/l

				Value/Result	
Ref	**Study type**	**Endpoint**		**D**	**US**
EF-W	chronic, fathead minnow	AI	NOEC	*	< 3.53 µg/l
EF-X	chronic, fathead minnow	AI	LC_{50}	10.6 µg/l	*
EF-X	chronic, fathead minnow	AI	NOEC	0.66 µg/l	*
EF-X	chronic, fathead minnow	AI	NOEL	1.48 µg/l	1.48 µg/l
EF-X	chronic, fathead minnow	AI	LOEC	2.71 µg/l	2.71 µg/l
EF-Y	prolonged, rainbow trout	FM		*	-
EF-Z	prolonged, rainbow trout	AI	NOEC	0.06 mg/l	-
EF-Z	prolonged, rainbow trout	AI	LOEC	0.19 mg/l	-
Daphnia					
EF-a	acute, D. magna	AI	LC_{50}	0.01 mg/l	*
EF-a	acute, D. magna	AI	NOEC	0.035 mg/l	*
EF-b	acute, D. magna	M	LC_{50}	3.28 mg/l	2.59 ppm
EF-b	acute, D. magna	M	NOEC	1.34 mg/l	1.08 ppm
EF-c	acute, D. magna	M	LC_{50}	> 100 mg/l	> 100 ppm
EF-d	acute, D. magna	FM	LC_{50}	*	3.38 mg/l
EF-e	acute, D. magna	AI	LC_{50}	0.08 mg/l	-
EF-e	acute, D. magna	AI	NOEC	0.03 mg/l	-
EF-e	acute, D. magna	M		*	-
EF-f	acute, D. magna	FM		*	-
EF-g	chronic, D. magna	AI	LC_{50}	0.04 mg/l	*
EF-g	chronic, D. magna	AI	LOEC	0.02 mg/l	*
EF-g	chronic, D. magna	AI	NOEC	< 0.02 mg/l	< 0.02 mg/l
EF-h	chronic, D. magna	AI	LOEC	2.21 µg/l	2.21 µg/l
EF-k	chronic, D. magna	FM		*	-
Other non-target species					
EO-A	Earthworm acute toxicity	AI	LC_{50}	50 mg/kg	-
Phytotoxicity to non-target plants; algae, growth inhibition					
EP-B	Algae, growth inhibition	AI	NOEC	0.032 mg/l	-
EP-B	Algae, growth inhibition	AI	EC_{50}	0.09 mg/l	-
EP-A	Algae, growth inhibition	AI	NOEC	*	-
EP-C	Algae, growth inhibition	FM	NOEC	*	-

- study not listed in that country's bibliography
***** study listed but information missing in that country's review
AI active ingredient
FM formulated product
M metabolite(s)

Reference code for test areas:

F - Fate and behaviour in the environment
E - Ecotoxicology:
EB - Birds/avian testing
EF - Fish including Daphnia
EO - Other non-target species (only earthworms)
EP - Non-target plants (only algae, growth inhibition)

Table 2. Test Guideline, GLP and Validity

	Test Guideline		GLP?		Valid?	
Ref	**D**	**US**	**D**	**US**	**D**	**US**
FATE AND BEHAVIOUR IN THE ENVIRONMENT						
Hydrolysis						
F-A	*	-	*	-	*	-
F-B	*	EPA 161-1	*	-	*	yes
F-C	*	EPA 161-1	*	-	*	yes
F-D	*	EPA 161-1	*	-	*	yes
F-E	-	*	-	*	-	*
Photodegradation in water						
F-E	-	*	-	*	-	*
F-F	*	EPA 161-2	*	*	*	no
F-G	*		*	*	*	yes
Soil metabolism						
F-E	-	*	-	*	-	yes
F-K	* *	EPA 162-1 EPA 162-2	* *	* *	* *	yes yes
F-L	*	-	*	-	*	-
F-M	*	-	*	-	*	-
F-N	*	-	*	-	*	-
F-O	*	-	*	-	*	-
F-V	*	-	*	-	*	-
F-W	-	EPA 162-4	-	*	-	yes
Mobility/Leaching						
F-E	-	*	-	*	-	*
F-Q	BBA	-	*	-	*	-
F-R	BBA	*	*	*	*	no (EPA-requirem.)
F-S	BBA	*	*	*	*	no (EPA-requirem.)
F-T	*	EPA 163-1	*	*	*	yes
F-U	*	-	*	-	*	-
F-V	*	-	*	-	*	-
F-Y	-	*	-	*	-	yes

Test Guideline			GLP?		valid?	
Ref	**D**	**US**	**D**	**US**	**D**	**US**
Adsorption/desorption in soil						
F-E	-	*	-	*	-	*
F-P	*	EPA 163-1	*	*	*	no
F-W	-	EPA 162-4	-	*	-	yes (water/sedim)
F-X	-	*	-	*	-	no
F-Z	-	*	-	*	-	*
Bound residues						
F-K	*	EPA 162-1	*	*	*	yes
	*	EPA 162-2	*	*	*	yes
Field dissipation						
F-M	*	EPA 164-1	*	*	*	yes
F-b	-	EPA 165-2	-	*	-	yes
F-E	-	EPA 164-1	-	*	-	yes
ECOTOXICOLOGY						
Avian testing						
EB-A	*	EPA 71-1	*	*	*	yes
EB-B	*	EPA 71-2	*	*	*	partial
EB-C	*	EPA 71-2	*	yes	*	yes
EB-D	*	*	*	*	*	*
EB-E	*	EPA 71-2	*	*	*	yes
EB-F	*	-	*	-	*	-
EB-G	*	EPA 71-4	*	*	*	no
EB-H	*	EPA 71-4	*	yes	*	partial
EB-I	*	*	*	*	*	*
EB-K	-	EPA 71-2	-	yes	-	yes
EB-L	-	EPA 71-2	-	yes	-	partial
EB-M	-	EPA 71-2	-	yes	-	partial
EB-N	-	*	-	*	-	*
EB-O	-	*	-	*	-	*
EB-P	-	*	-	*	-	*
EB-S	-	EPA 71-4	-	*	-	no
EB-Q	-	EPA 71-2	-	yes	-	partial
EB-R	-	EPA 71-2	-	yes	-	partial
EB-X	-	EPA 71-4	-	yes	-	yes
EB-Z	-	EPA 71-4	-	yes	-	yes

Test Guideline			GLP?		valid ?	
Ref	**D**	**US**	**D**	**US**	**D**	**US**
Aquatic testing						
Fish						
EF-A	*	*	*	*	*	partial
EF-B	*	yes	*	*	*	yes
EF-C	*	EPA 72-1	*	*	*	yes
EF-D	*	EPA 72-1	*	*	*	yes
EF-E	*	EPA 72-1	*	*	*	yes
EF-F	*	EPA 72-1	*	*	*	yes
EF-G	*	EPA 72-1	*	yes	*	yes
EF-R	-	EPA 72-3	-	*	-	yes
EF-S	-	EPA 72-3	-	yes	-	yes
EF-U	-	yes	-	yes	-	yes
EF-V	-	yes	-	yes	-	yes
EF-W	*	EPA 72-4	*	yes	*	yes
EF-X	*	yes	*	yes	*	yes
EF-Z	*	-	*	-	*	-
Daphnia						
EF-a	*	-	*	-	*	-
EF-b	*	EPA 72-2	*	*	*	yes
EF-c	*	EPA 72-2	*	*	*	yes
EF-d	*	EPA 72-2	*	yes	*	yes
EF-e	*	-	*	-	*	-
EF-g	*	EPA 72-4	*	yes	*	yes
EF-h	*	EPA 72-4	*	yes	*	yes
Other non-target species						
EO-A	(not OECD)	-	*	-	*	-
Phytotoxicity to non-target plants; algae; growth inhibition						
EP-B	*	-	*	-	*	-
EP-B	*	-	*	-	*	-
EP-A	*	-	*	-	*	-
EP-C	*	-	*	-	*	-

- \- study not listed in that country's bibliography
- * study listed but information missing in that country's review

Table 3. Citation Frequency

Study type	Total number	Cited by		
		US and D	only D	only US
Hydrolysis	5	3	1	1
Photodegradation in water	3	1	1	1
Soil metabolism	8	1	5	2
Mobility/leaching	8	3	3	2
Adsorption/desorption in soil	5	1	-	4
Bound residues	1	1	-	-
Field dissipation	3	1	-	2
Avian testing	20	8	1	11
Fish	14	9	1	4
Daphnia	7	5	2	-
Algae	4	-	4	-
Earthworms	1	-	1	-
Sum for fate	33	11	10	12
Sum for ecotoxicology	45	22	9	15
Overall sum	78	33	19	27
	100%	42%	24%	35%

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EF-h Smith, G. (1989) W108 Flow-through Chronic Toxicity of Amitraz to Daphnia magna: Lab Project Number: ENVIR/108L. Unpublished study prepared by Battelle Columbus Division. 145 p. Review date: 3/90. EPA-Reference 41288701

EF-k Knacker, T.; A Study of the Chronic Toxicity to Daphnia of Mitac 20 EC.- W 148, Schering AG, Aug. 1991, Battelle-Institut e.V.

Other non-target organisms; earthworms

EO-A (1) WEIGHTON, D. M. (1974): The Effect of BTS 27419 on Earthworms (Lumbricus terrestris). Schering Agrochemicals Ltd., Chesterford Park Research Station.

Non-target plants; algae, growth inhibition

EP-A Oldersma, H. et al.; The Effect of the Product Amitraz Technical on the Growth of Green Algae (Scenedesmus subspicatus). W 64, Schering AG, Jan. 1985

EP-B Knacker, T.; A Study of the Toxicity to Algae (Selenastrum capricornutum) of Amitraz Technical.- W 158, Schering AG, May 1992, Battelle-Institut e.V.

EP-C Knacker, T.; A Study of the Toxicity to Growth and Reproduction of the Aquatic Plant (Selanastrum capricornutum) of Mitac 20 EC.- W 149, Schering AG, August 1991, Battelle Institut e.V.

PART 2: TOXICOLOGY AND METABOLISM

2.1 Types of data reviews

The data reviews produced by Germany, Canada and FAO were summarised in one document, respectively, with a similar content and length. The US EPA has produced different documents (Toxicology Reviews, Peer Reviews, Data Evaluation Reports) with different structures and volumes. The language was English in all reviews. Germany and Canada have reviewed the endpoints in the same order:

A: Acute Testing;
B: Subchronic Testing;
C: Developmental Toxicology.

The US EPA and FAO have used another order for their reviews of toxicological test areas. A harmonization of structure and form in data reviews would be helpful to compare pesticide re-registration reviews between different countries.

The reviews have covered individual studies and the same test areas for toxicological testing. The reviews of Germany, the US and FAO contain a summary of reviewer's conclusions about the toxicological data of Amitraz, which was not included in the review of Canada. The greatest similarities were observed between Germany and Canada and the greatest differences between the US and the other participating countries.

2.2 Test areas, studies addressed

Acute testing

Ten percent of the 40 studies in test area acute toxicity were reviewed by all participants. Forty percent of studies were reviewed by only one country.

For the test areas listed in Table A (see Appendix 3) for acute testing all countries have reviewed data. In most cases different studies were reviewed for the various test areas. Mostly, it was not possible to identify studies, which were cited for specific test areas and/or endpoints. Especially if more than one study regarding the same test area is cited (and if the study was not available in the lead country), the study could not be identified, which was used to estimate the endpoint in the review. In other cases (e.g. skin sensitisation) an identification of studies was helpful to clarify the different conclusions, which were made in the reviews (e.g. Germany: Study-Nr. A22(1988) -> extreme skin sensitiser; Canada: Study-Nr. A36 -> skin sensitiser; US: Study-Nr. A5(1971) -> no skin sensitisation). In this test area different studies were submitted to the participating countries and therefore they have identified a different hazard regarding skin sensitisation. The LD_{50} for inhalation toxicity was differently specified with greater than 65 mg/l (6h) using the nominal concentration by Germany and FAO and with 2.4 mg/l (6h) using the actual concentration by gravimetric estimation by the US. All participants cited the same inhalation study (A4).

Information on the quality of the data was not included in the reviews regarding acute testing.

Subchronic testing

Thirty-three percent of the 15 studies in test area subchronic toxicity were reviewed by all participants. Only two studies were reviewed by one country.

All countries reviewed data in the five test areas listed in Table B for subchronic testing. In most cases the same studies were reviewed by more than two participants. The dog was the most sensitive species in subchronic testing with a NOEL of 0.25 mg/kg b.w. The Central Nervous System (CNS) was identified as the main target by all participants.

Information on the quality of the data was not included in the reviews regarding subchronic testing.

Developmental toxicity and reproductive studies

Three of the eight studies in the test area developmental toxicity and reproductive studies were reviewed by all participants. Five studies were reviewed by two countries. One important result of the Pilot Project was to show that two teratogenicity studies on rats (C5, C6) and two teratogenicity studies on rabbits (C7, C8) from 1987 were only submitted in the US and Canada. Germany and the FAO reviewed only older studies, which were evaluated as inadequate by Canada. The participants identified different targets and NOEL's for maternal and developmental toxicity. Nevertheless, all paticipants had the same hazard assessment for this test area, and none proposed classification of Amitraz as a "developmental teratogen".

Metabolism testing

Fifteen percent of the 39 studies in the test area metabolism testing were reviewed by all participants. Twenty-nine of studies were reviewed only by one country.

The field of metabolism testing showed the greatest variety in study designs, used species and interpretations of results. A clear concept for hazard estimation can not be derived. For a comparable interpretation of metabolism studies, a harmonised guidance document would be necessary. By all differences the main points were recognised by all countries (e.g. oral absorption greater than dermal; urinary excretion greater than faecal; no species differences in metabolism). Regarding the aspects of animal protection not all studies with the tested species would be necessary.

Chronic testing

Three of the seven studies in the test area chronic toxicity were reviewed by all participants. These included long term studies in rats (E1), mice (E2), and dogs (E4). Only two studies were reviewed by one country.

Countries agreed that the dog was the most sensitive species in chronic testing with a NOEL of 0.25 mg/kg b.w. The Central Nervous System (CNS) was identified by all participants as the main target for chronic toxicity. No cancerogenic action was identified in the rat study.

Countries disagreed, however, in their hazard assessment based on the long term studies in mice. The US EPA classified Amitraz as a Group C, possible human carcinogen. This classification was based upon the increased tumor incidences in liver, lung and lymphoreticular system. The other participating countries did not consider these increased tumor incidences as biologically significant. The reasons were discussed in the reviews, e.g. overestimation of neoplastic lesions by some pathologists, lack of a dose/effects relationship, and no significant differences to historical control data incidences. One main reason for this different interpretation of the same studies was the non-uniform toxico-pathologic practice in the assessment of histological findings, which is recently not included in any quality control. The "over diagnosis" of lymphoreticular tumors in female mice in the 80-week study (C1) was based on the different diagnostic criteria used by the investigating pathologists for neoplastic lesions in mice. For example, the pathologic lesion on the same slide (1320/75; Anim.-Nr. 673/50) was identified by Dr. Lancaster as "lymphoid hyperplasia", by Dr. Kakuk as "malignant lymphoma", and in the original report as "lymphosarcoma". The result was that Dr. Lancaster and Dr. Kakuk reported at the 400 ppm dose level 35% "lymphoreticular tumors" in comparison to 49% in the Boots original report. The percentage of "lymphoreticular tumors" at this dose level was estimated between 24% and 61% (in the control group between 14% and 23%) by various pathologists in six reports from the same study. Many other examples are available. These different estimations of the carcinogenic risk of Amitraz show the necessity for harmonisation of diagnostic criteria and terminology in toxico-pathology, a process that has beeen started e.g. the US Society of Toxicological Pathology (STP) and the Fraunhofer-Institut in Hannover, among others. The differences in interpretation of chronic tests were most important in the countries' differing assessments of the pesticide's hazard.

Mutagenicity

Fourteen percent of the 21 studies in the test area mutagenicity testing were reviewed by all participants. Nineteen percent of studies were reviewed only by one country.

In the test area mutagenicity testing a similar situation was observed as reported for acute testing. A great number of studies with active ingredient and metabolites were performed and different studies were submitted to the participating countries. The tests failed to demonstrate any potential for mutagenic activity such as gene mutations, chromosomal damage or DNA aberrations, so that countries' hazard assessment for mutagenicity testing was the same.

Neurotoxicity testing

Seven studies regarding neurotoxic effects were reviewed by Germany, but they were mostly publications without raw data. No neurotoxic testing data were submitted in the US, Canada or FAO. These participants discussed the data for related studies in the other sections. Nevertheless all countries emphasized the neurotoxic potential of Amitraz, especially the behavioural effects which were seen in acute, subacute and chronic tests as well as in special studies on pharmacological activity.

Other testing

Only 8% of the 38 studies in this open test area were reviewed by all participants. Sixty-six percent of studies were reviewed only by one country.

A great variety of studies, mostly from the literature, were reviewed. The same targets (e.g. reduced blood pressure, bradycardia, hypothermia, hormonal imbalances, prolongation of oestrus) were discussed by all participants. These effects were seen in acute, subacute and chronic tests as well as in special studies. This section should be discussed together with the neurotoxic chapter as well as with other test areas such as immunotoxicity if necessary.

Medical data

None of the 10 studies in the test area medical data were reviewed by all participants. Sixty-six percent of studies were reviewed only by one country. Canada did not include a special section for medical data. The investigations on human beings were reviewed elsewhere, for eaxample under acute or metabolism testing. The other participants called this section "human exposure" (US), "observations in humans" (FAO) or "human data" (Germany). Most studies were submitted only to one country. The investigations on human beings appeared to have a lower quality than the animal experiments, which were mostly performed under SPF-conditions. Depending on the study submitted, possible effects on humans were described, e.g. drowsiness, skin irritation, bradycardia, hypothermia.

2.3 Identification of information used to identify hazard

2.3.1 Information used to assess the pesticide’s hazard

The most sensitive species to toxicological effects of Amitraz was the dog with an overall no effects level of 0.25 mg/kg b.w. in both chronic and subchronic studies. The dose levels tested in dogs were 0.1; 0.25; 1.0; 4.0 mg/kg b.w. in repeated dose toxicity studies. Rats and mice have a lower sensitivity in these studies with an overall NOEL of 3 and 2.5 mg/kg b.w., respectively. Amitraz has shown dose-response relationships in most affected parameters.

Amitraz is rapidly absorbed after oral gavage and poorly absorbed after dermal application. Accumulation or persistence in mammals was not described. Amitraz is completely metabolised and is rapidly excreted mainly via urine. The metabolism is qualitatively similar in rats, mice, dogs, cats, cattle, monkeys and humans.

For a great number of investigations it is not possible to identify the date of the study, because older studies were often submitted with a newer date and title. The majority of toxicological studies with Amitraz were performed between 1971 and 1973 as well as between 1983 and 1987.

2.3.2 Comparison of countries' conclusions

The most important target organ in toxicological tests with Amitraz on laboratory animals was the Central Nervous System (CNS). The Cardiovascular System and the liver were also important targets. These targets were identified by all participating countries.
The most important route of exposure was the oral route. Persistence problems were of minor importance.

Countries gave the greatest weight to effects seen in chronic and carcinogenicity studies in mice, followed by skin sensitisation and special reproduction studies. The most significant problems for human health were the different interpretations of the increased incidences of neoplastic lesions. The US EPA has classified Amitraz as Group C, possible human carcinogen, whereas the other participating countries have not assessed these increased tumor incidences as a potential risk for human health.

2.4 Comparison of countries' hazard assessments

A total of 190 toxicological studies was reviewed by the participating countries. Figure 1 (see Appendix 2) shows the number of studies cited by each country. The percentage of the total available studies reviewed by each country was 74% for Germany, 50% for the US, 50% for FAO and 36% for Canada. Only 14% of the 190 studies was reviewed by all participating countries. Approximately 25% was reviewed three times, and another 25% was reviewed twice. However nearly 40% of the cited studies were reviewed by only one country. It could not be determined whether these studies were submitted to other countries.

To a large extent countries have reported the same endpoints. The frequency (see Figure 2 in Appendix 2) and number of reviewed studies in the various test areas were highly variable, listed in Tables A to I. Phase 2 of the Pilot Project determined for each study whether it was cited by a participating country. The greatest number of studies were cited in test areas acute toxicity and metabolism testing, as shown in Figure 3. This figure also shows that in the test areas developmental toxicity and chronic testing, the fewest studies were reviewed.

The participating countries have focused their reviews on the same endpoints in assessing amitraz's hazard. They have drawn the same conclusions about the acceptable exposure levels, e.g. ADI-value. They have not estimated the same hazard regarding the most important endpoint carcinogenicity nor selected the same cancer classification. Regarding the other endpoints, countries drew similar conclusions in assessing the pesticide's hazard.

2.5 Conclusions and recommendations

- The participating countries focused their reviews on the same endpoints in assessing the pesticide's hazard. The frequency and number of reviewed studies in the various test areas were variable both between test areas and participants.

- A harmonisation of structure and form in data reviews would be helpful to compare pesticide re-registration reviews between different countries.

- In many cases the cited studies could not be identified in the reviews, if these studies were not submitted to the lead country. Therefore a harmonisation of citation format in the reviews would be necessary.

- For a comparable interpretation of metabolism studies a harmonised guidance document would be necessary.

- A guidance document is also necessary for diagnostic criteria and terminology in toxico-pathology especially for a harmonised interpretation of chronic studies and a harmonised classification of carcinogenic substances.

- A separate discussion of neurotoxic endpoints should be replaced by a combined assessment of "specific effects" in a section on "other testing" that includes neurotoxicity, immunotoxicity, pharmacological effects, hormonal changes etc.

- The investigations on human beings were of lower quality than in the animal experiments which were mostly performed under SPF-conditions. A higher quality standard in this test area would be necessary.

Appendices on toxicology

Appendix 1. Figures

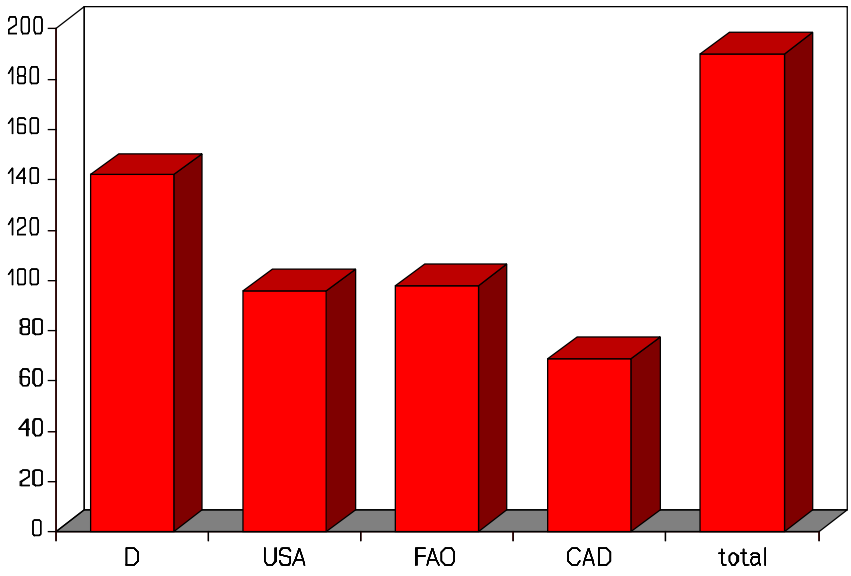


Fig. 1. Number of the 190 Toxicological Studies on Amitraz (total), which were Reviewed by Germany (D), the US, FAO, Canada (CAD)

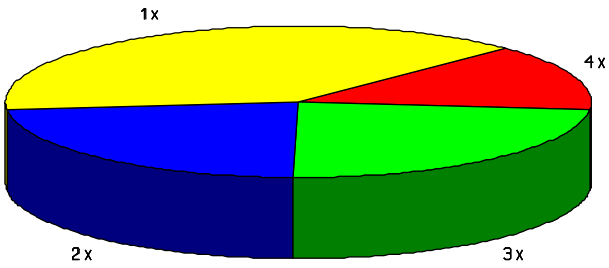


Fig. 2. Citation Frequency of the 190 Toxicological Studies Reviewed for Amitraz by Germany, the US, Canada and FAO

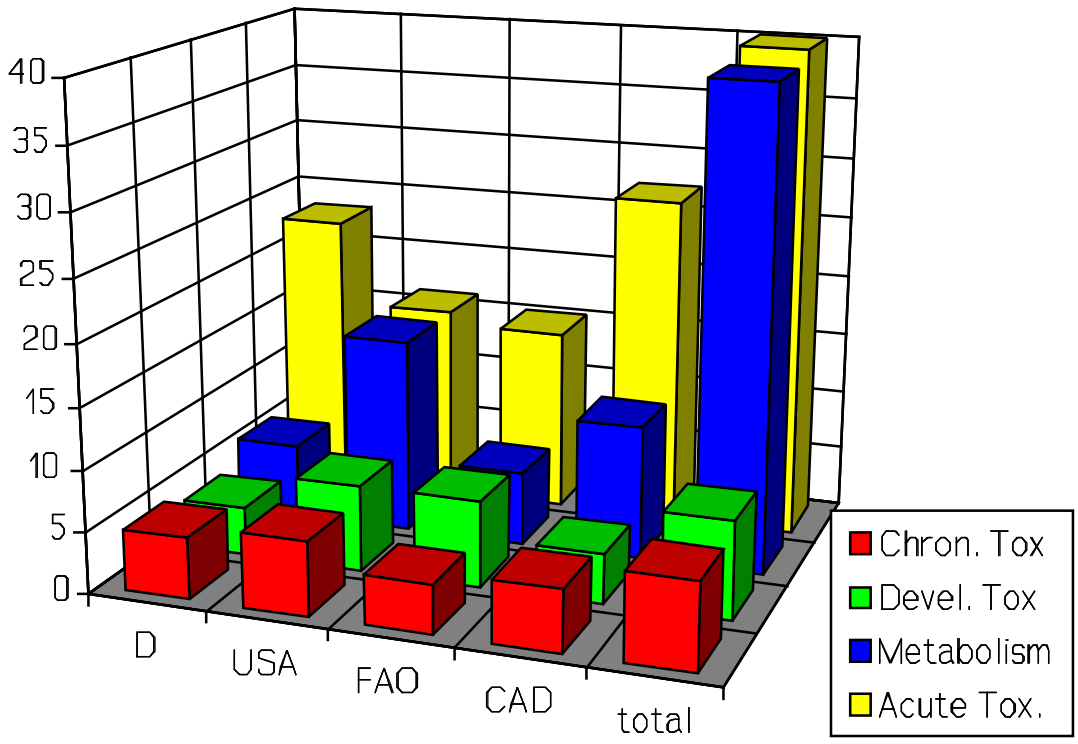
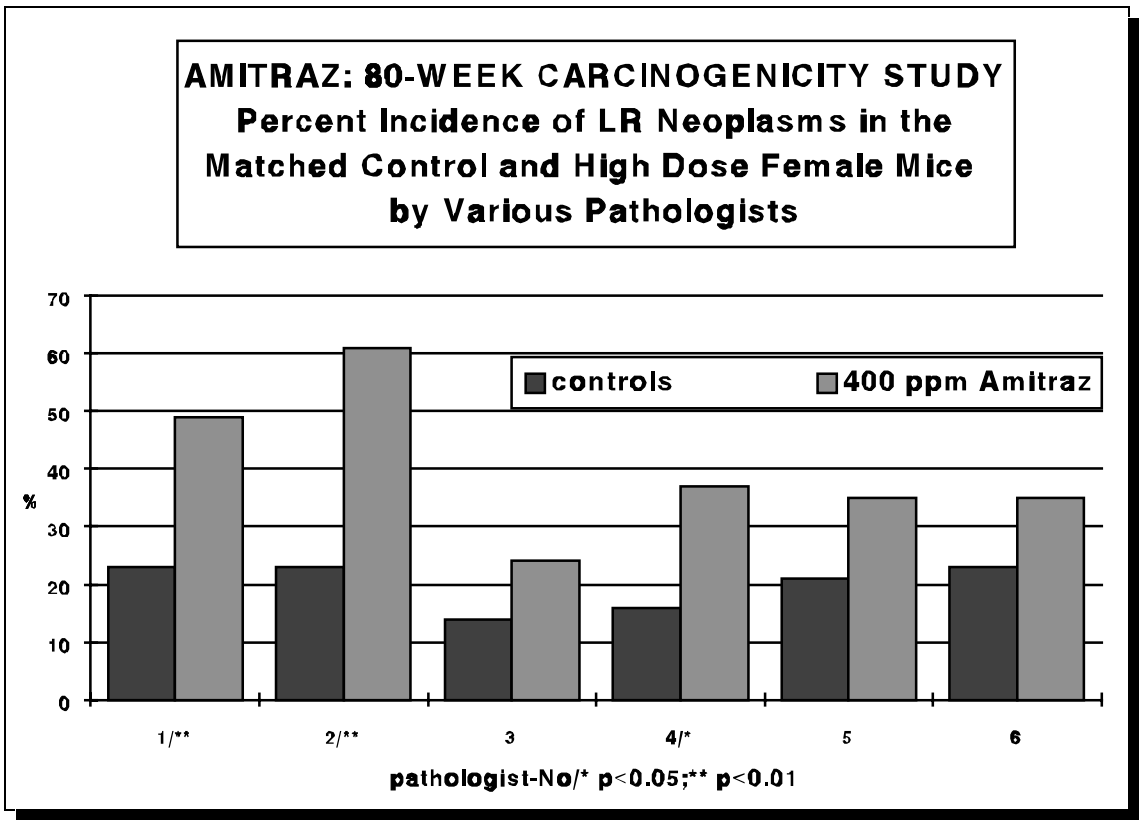


Fig. 3. Number of Toxicological Studies on Amitraz, which were Reviewed by Germany (D), the US, FAO, Canada (CAD) in the Identified Test Areas Both with the Highest (Acute Toxicity, Metabolism) and the Lowest (Developmental Toxicity, Chronic Toxicity) Frequency



80-WEEK CARCINOGENICITY STUDY OF AMITRAZ IN FEMALE MICE

COMPARISON OF INDIVIDUAL ANIMALS AND SAME SLIDE NUMBERS WITH LYMPHORETICULAR TUMORS AS IDENTIFIED IN THE REPORTS OF THREE PATHOLOGISTS

Animal-No.	**Treatment**	**Pathologist No.5**	**Pathologist No. 1**	**Pathologist No. 6**
669/29	Control	Lymphadenitis	Probable lymphosarcoma	Lymphadenitis and pancreatitis
673/50	Control	Lymphoid hyperplasia	Lymphosarcoma	Malignant lymphoma
664/3	Control	Malignant lymphoma	Lymphoid hyperplasia	Malignant lymphoma
696/165	400 ppm	Lymphoid hyperplasia	Lymphosarcoma	Malignant lymphoma
700/185	400 ppm	Lymphadenitis	Lymphosarcoma	Lymphadenitis
703/198	400 ppm	Lymphadenitis containing plasma cells and Russel Bodies	Leukaemia lymphosarcoma	Plasma cell myeloma

Appendix 3. Tables

Comparison of Endpoints Reported in Countries' Data Reviews on the Active Ingredient

-- TABLE A --

Ref.A	ACUTE TESTING		D	US	CND	FAO
	Citation: 4= 4x; 9= 3x; 11= 2x; 16= 1x	Nr of studies: 40	23	16	15	27
	Citation: 10% 4x; 22% 3x;28% 2x; 40% 1x	% of studies	58	40	38	68
A1,A2	Acute oral toxicity (rat)	LD_{50} (mg/kg bw)	515-800	515-531	400-938	app.800
	Acute oral toxicity (sensitivest species)	LD_{50}	dog	dog	dog, pig	dog
A2	Acute dermal toxicity (rat)	LD_{50} (mg/kg bw)	> 1600			> 1600
A24	Acute dermal toxicity (rabbit)	LD_{50} (mg/kg bw)		> 200*		
A36	Acute dermal toxicity (rat/rabbit*)	LD_{50} (mg/kg bw)			> 1600	
A4	Acute inhalation toxicity (rat)	LD_{50} (mg/l, 6h)	> 65(1)	2.4(2)	-	65(1)
A5	Skin irritation (rabbit)	irritant	no	-	minimal	no
A8	Eye irritation (rabbit)	irritant	minimal			
A32	Eye irritation (rabbit)	irritant		no	minimal	no
A5	Skin sensitisation (guinea pig)	skin-sensitizer				no
A22	Skin sensitisation (guinea pig)	skin-sensitizer	extreme			
A36	Skin sensitisation (guinea pig)	skin-sensitizer		-	yes	
	Acute oral toxicity, clinical signs in rats	CNS depression ataxia, hyperactivity dysponea anorexia, emesis hypothermia, bradycardia	x x x x x	x x x x x x	x x x x x x	x x x x

((1) nominal concentration (2) actual concentration by gravimetric estimation)

-- TABLE B --

Ref.B	SUBCHRONIC TESTING		D	US	CND	FAO
	Citation: 5= 4x; 5= 3x; 3= 2x; 2= 1x	Nr of studies: 15	14	8	8	13
	Citation: 33% 4x; 33% 3x;20% 2x; 14% 1x	% of studies	93	53	53	87
B3	Repeated dose dermal (rabbit, 21 days)	NOEL (mg/kg bw)	< 50	< 50	-	< 50
B3		Targets	CNS, heart	CNS, heart, testes	-	testes
B2	Repeated dose inhalation (rat, 28 days)	NOEL (mg/l air)	0.01	0.01	-	0.01
B2		Targets	CNS	CNS, blood	-	CNS, blood
B4	Subchronic oral (rat, 90 days)	NOEL (mg/kg bw)	3	3	3	3
B4		Targets	CNS, liver, thymus, adrenals	CNS, liver, adrenals	CNS, platelets	CNS, platelets, kidney
B10	Subchronic oral (mice, 90 days)	NOEL (mg/kg bw)	3	3	3	3
B10		Targets	liver	liver	liver	liver
B7	Subchronic oral (dog, 90 days)	NOEL (mg/kg bw)	0.25	0.25	0.25	0.25
B7		Targets	CNS, liver, adrenals	CNS, liver, adrenals	CNS, CVS	CNS, liver, adrenals
	Subchronic toxicity (sensitivest species)	NOEL	dog	dog	dog	dog

-- TABLE C --

Ref. C	DEVELOPMENTAL TOXICITY AND REPRODUCTIVE STUDIES		D	US	CND	FAO
	Citation: 3= 4x; 0= 3x; 5= 2x; 0= 1x	Nr of studies: 8	4	7	7	4
	Citation: 38% 4x; 0% 3x;62% 2x; 0% 1x	% of studies	50	88	88	50
	Teratogenicity (rat)					
C3	- maternal toxicity	NOEL (mg/kg bw)	12			-
C3	- developmental toxicity	NOEL (mg/kg bw)	12			3
C3	- developmental effects	Targets	no			no
C5,C6	- maternal toxicity	NOEL (mg/kg bw)		5	7.5	
C5,C6	- developmental toxicity	NOEL (mg/kg bw)		5	7.5	
C5,C6	- developmental effects	Targets		decreased litter size	no	
C4	Teratogenicity (rabbit)					
C4	- maternal toxicity	NOEL (mg/kg bw)	5			5
C4	- developmental toxicity	NOEL (mg/kg bw)	5			-
C4	- developmental effects	Targets	increased abortion			no
C7,C8	- maternal toxicity	NOEL (mg/kg bw)		3	12	
C7,C8	- developmental toxicity	NOEL (mg/kg bw)		3	< 3	
C7,C8	- developmental effects	Targets		decreased implantation, viability	no	

Ref. C	DEVELOPMENTAL TOXICITY AND REPRODUCTIVE STUDIES		D	US	CND	FAO
C1	Multi-generation reproduction (rat)	NOEL (ppm)	15	15	< 15*	15
C1	- maternal/developmental toxicity	NOEL (mg/kg bw)	1.6	1.5	1.6	
C1,C2	- developmental effects	Targets	neonatal mortality	neonatal mortality, decreased viability, lactation	neonatal mortality	neonatal mortality, decreased fertility, via-bility
H10,	Prolongation of oestrus in rats		x	x	x	x
H40	Prolongation of oestrus in mice		x	x	x	x
H43	Increased proestrus, decreased diestus without effect of estrus period in mice			x		

* regarded as a minimum effect level

-- TABLE D --

Ref. D	METABOLISM TESTING		D	US	CND	FAO
	Citation: 6= 4x; 16= 3x; 6= 2x; 11= 1x	Nr of studies: 39	27	27	19	22
	Citation: 15% 4x; 41% 3x;15% 2x; 29% 1x	% of studies	69	69	49	56
D24	Absorption	dermal	poorly	8x < oral(pig)	slow	
D24	Recovery	dermal	7% (pig); 25-40% (rat)	50% (rat)	12% (pig) 30% (dog)	50% (rat)
D1,D2	Absorption	oral	rapid	rapid	rapid	peak 1h after dosing
D1,D2	Recovery, urine	oral	urine > feces	79-82% (rat)	77-88% (rat)	53-85% (rat)
D1,D2	Recovery, feces	oral	feces > urine	17% (rat)	4-9% (rat)	17-47% (rat)
D1,D2	Main excretion pathway	rat	urine	urine	urine	urine
D1,D2	Main metabolic pathway	rat	acid hydrolysis	acid hydrolysis	acid hydrolysis	acid hydrolysis
D1,D2	Main metabolites	in urine	BTS 39098, FBC 31158	BTS 39098, BTS 31158	BTS 39098, FBC 31158	BTS 28369
D1	Highest residues	single application	liver, kidneys	liver-bile, eye, adrenals, kid-neys	liver, eye	liver, kidney, muscle
D16	Species differences	metabolism	no (human, mouse, rat, bovine, cat, baboon)	no (human, mouse, rat, dog, baboon)	no (human, mouse, rat, bovine, cat, baboon, dog)	no (mouse, rat, bovine, cat, dog)
D14	Sex differences	metabolism	no	no	no	
D25	Sex differences	metabolism				yes (urine metabolites)

-- TABLE E --

Ref. E	CHRONIC TESTING		D	US	CND	FAO
	Citation: 3= 4x; 2= 3x; 0= 2x; 2= 1x	Nr of studies: 7	05	06	04	05
	Citation: 44% 4x; 28% 3x;0% 2x; 28% 1x	% of studies	71	86	57	71
E4	Chronic oral (dog)	NOEL (mg/kg bw)	0.25	0.25	0.25	0.25
E4		Targets	CNS, body temperature	CNS, body temperature	CNS, body temperature	CNS
E1	Chronic oral (rat)	NOEL ppm (mg/kg bw)	50(2.5)	50	50(2.5)	50(3.0)
E1		Targets	behaviour, food intake	behaviour, food intake, body weight	behaviour, body weight	behaviour, food intake
E2,E3	Chronic oral (mice)	NOEL ppm (mg/kg bw)	25(2.3)	< 25	25(2.3)	25(2.5)
E2, E3, E5		Targets	behaviour, survival, food intake, body weight, liver, lung, stomach	behaviour, survival, food intake, body weight, liver, lung, stomach, lymphoretic. system	behaviour, survival, food intake, body weight, liver, lung, stomach	food intake, liver, lymphoretic. system
	Classification	Carcinogenicity	no	yes/Group C*	no	no

* This classification was based upon the increased tumor incidences in liver, lung and lymphoreticular system in mice.
The other participating countries have not considered these incidences as significant for a classification.

-- TABLE F --

Ref. F	MUTAGENICITY		D	US	CND	FAO
	Citation: 3= 4x; 5= 3x; 9= 2x; 4= 1x	Nr of studies 21	19	14	8	8
	Citation: 14% 4x; 24% 3x;43% 2x; 19% 1x	% of studies	90	67	38	38
F1	Gene mutations		no	no	no	no
F2	Gene mutations		no			no
F3	Gene mutations		no			
F4	Gene mutations		no	no	no	
F5	Gene mutations		no	no		
F6	Gene mutations		no	no		
F7	Gene mutations		no	no		
F8	Gene mutations		no	no		no
F9	Gene mutations		no	no	no	
F10	Gene mutations		no	no		
F11	Chromosomal damage		no	no		
F12	Chromosomal damage		no	no		no
F16	Chromosomal damage		no	no	no	no
F17	Chromosomal damage		no	no	no	no
F18	Chromosomal damage		no			
F13	DNA aberration / gene damage		no			no
F14	DNA aberration / gene damage		no	no	no	
F15	DNA aberration / gene damage		no			
F19	DNA aberration / gene damage		no		no	
	Classification	mutagenicity	no	no	no	no

-- TABLE G --

Ref. G	NEUROTOXICITY TESTING		D	US	CND	FAO
	Citation: 0= 4x; 0= 3x; 2= 2x; 5= 1x	Nr of studies: 7	7	0	2	0
	Citation: 0% 4x; 0% 3x;29% 2x; 71% 1x	% of studies	100	0	29	0
G4	Enhancement of excitatory processes		x			
G4	Reduction of inhibitory processes		x			
G6	Alpha2-adrenergic receptor agonist		x		x	
G7	Alpha2-adrenergic receptor agonist		x		x	
H15	Altered neurotransmitter levels*		x			
H15	Changes in neuro-endocrine feedback*		x			
A2	Behavioural effects**		x	x	x	x
	Classification	neurotoxic	yes	yes	yes	yes

** Behavioural effects were not only cited in special neurotoxicity studies.
They were mostly observed in acute toxicity studies on different species e.g. in Ref. A2

-- TABLES H and MH --

Ref. H	OTHER TESTING		D	US	CND	FAO
	Citation: 3= 4x; 7= 3x; 3= 2x; 25= 1x	Nr of studies: 38	30	15	05	14
	Citation: 8% 4x; 18% 3x;8% 2x; 66% 1x	% of studies	79	39	13	37
H15, H38	Reduced blood pressure		x	x	x	x
H15, H38	Bradycardia		x	x	x	x
H15, H25	Hypothermia		x	x	x	x
H31	Hyperglycaemia		x	x		
H31	Glucose intolerance / hypoinsulinemia		x	x		
H12, H13	Hormonal imbalances		x	x	x	
H10, H40	Prolongation of oestrus		x	x	x	x
H24	Antidiuretic action					x
H37	Inhibition of ileum contractions		x			
Ref.MH	**MEDICAL DATA**		**D**	**US**	**CND**	**FAO**
	Citation: 0= 4x; 1= 3x; 5= 2x; 4= 1x	Nr of studies: 10	8	3	2	4
	Citation: 0% 4x; 10% 3x;50% 2x; 40% 1x	% of studies	80	30	20	40
8	Vomiting and headache		x		x	
MH1	Local irritation of the skin		x	x		
MH3	Flushing of the skin		x	x(?)		x
D17	Drowsiness		x		x	
D17	Sedation, Dry mouth, Disorientation, Bradycardia, Hypertension, Hypothermia*			x	x	

-- TABLE I --

Ref. I	EVALUATION*	Endpoint	D	US	CND	FAO
	Citation: 0= 4x; 0= 3x; 1= 2x; 4= 1x	Nr of studies 5	5	0	0	1
	Citation: 0% 4x; 0% 3x;20% 2x; 80% 1x	% of studies	100	0	0	20
	Safety factor	to human studies	10			
		to dog studies	> 100	100		500
	ADI-value (mg/kg bw)		0.003	0.025		0.0005
	Maximum permitted intake (mg/day)	60 kg human		0.15		
	Guide value for drinking water (ul)		11			
	Maximum residue levels (mg/kg)	meat	0.05-0.1			0.05-0.2
		milk	0.01			0.01
		fruits	0.5	0.015(1)		0.5
	Labelling, classification		no	cancerogen, Group C	no	no

(1) in or on pears

***** Evaluation was not cited in special reference studies.

Summary Table

Toxicology and Metabolism

No.	**STUDY (Frequency)**	**4x**	**3x**	**2x**	**1x**	*****
A	ACUTE TESTING	04	09	11	16	40
B	SUBCHRONIC TESTING	05	05	03	02	15
C	DEVELOPMENTAL TOXICITY AND REPRODUCTIVE STUDIES	03	00	05	00	08
D	METABOLISM TESTING	06	16	06	11	39
E	CHRONIC TESTING	03	02	00	02	07
F	MUTAGENICITY	03	05	09	04	21
G	NEUROTOXICITY TESTING	00	00	02	05	07
H	OTHER TESTING	03	07	03	25	38
MH	MEDICAL DATA	00	01	04	05	10
I	EVALUATION	00	00	01	04	05
	TOTAL	*27*	*45*	*44*	*74*	*190*
No.	STUDY (Number)	D	US	CAN	FAO	*
A	ACUTE TESTING	23	16	15	27	40
B	SUBCHRONIC TESTING	14	08	08	13	15
C	DEVELOPMENTAL TOXICITY AND REPRODUCTIVE STUDIES	04	07	07	04	08
D	METABOLISM TESTING	27	27	19	22	39
E	CHRONIC TESTING	05	06	04	05	07
F	MUTAGENICITY	19	14	08	08	21
G	NEUROTOXICITY TESTING	07	00	02	00	07
H	OTHER TESTING	30	15	05	14	38
MH	MEDICAL DATA	08	03	01	04	10
I	EVALUATION	05	00	00	01	05
	TOTAL	*142*	*96*	*69*	*98*	*190*

* = Sum of reviewed reports

Appendix 4. REFERENCES

No.	STUDY	D	US	CH	FAO	*
A	**ACUTE TESTING**					
A1	WTox 5; Report T 3: BTS 27419: Comparison of the acute oral and intraperitoneal toxicities to rats. Shaw, J.W.; Date: Feb. 1973.	#	#	--	#	
A2	WTox 2; Report T 70: Acute toxicity studies on BTS 27419 an acaricide. Patton, D.S.G. and Sutton, M.M.; Date: 1974.	#	#	--	#	
A3	WTox 3; Report TXM 73041: BTS 27419: Acute oral toxicity to male and female rats. Shaw, J.W.; Date: Nov. 1973.	#	#	--	#	
A4	WTox 6; Report T 7: Acute inhalation toxicity to the rats of BTS 27419. Berczy, Z.S. et al.; Date: June 1972.	#	#	--	#	
A5	WTox 48; Report T 58: BTS 27419: Contact sensitisation in the guinea pig. Sutton, M.M.; Date: Jan. 1971.	#	#	--	#	
A6	WTox 4; Report T 4: BTS 27419: Acute intraperitoneal toxicity to rats. Shaw, J.W.; Date: Dec. 1971.	#	--	--	#	
A7	WTox 1; Report without number Experimental data on toxicity in animals; acute toxicity. Anon.; Date: without.	#	--	--	#	
A8	WTox 169; Report T 293: Technical Amitraz: Irritant effects on the rabbit eye. Liggett, M.P. and Smith, P.A.; Date: Nov. 1987.	#	--	--	--	
A9	WTox 46; Report T 12: Acaricides: RD 27419 and RD 27271. Acute toxicity to guinea pigs. Sutton, M.M.; Date: Nov. 1970.	#	--	--	#	
A10	WTox 129; Report T 9: RD 27271: Acute toxicity to rats; Sutton, M.M.; Date: May 1970.	#	--	--	#	
A11	WTox 130; Report T 10: RD 27271: Acute oral toxicity to mice. Sutton, M.M.; Date: May 1970.	#	--	--	#	
A12	WTox 133; Report T 18: Acute oral studies on triazid impurities. Lessel, B.; Date: Oct. 1971.	#	--	--	#	
A13	WTox 132; Report T 16: BTS 27271: Acute oral toxicity study in dog. Morgan, H. and Williams, G.A.H.; Date: Jan. 1973.	#	#	--	#	
A14	WTox 146; Report T 15: Comparison of the acute oral toxicities to rats of BTS 27419 and BTS 27919. Shaw, J.W.; Date: March 1973.	#	--	--	#	
A15	WTox 149; Report T 13: BTS 27419 metabolite: BTS 28369 acute oral toxicity to rats. Shaw, J.W. and Williams, P.A.; Date: Aug. 1973.	#	--	--	--	
A16	WTox 150; Report T 14: BTS 27419 metabolite: BTS 28369 acute oral toxicity to mice. Shaw, J.W. and Williams, P.A.; Date: Aug. 1973.;	#	--	--	--	
A17	WTox 151; Report T 17: BTS 28369: Acute oral toxicity study in dog. Morgan, H. and Shepherd, G.M.; Date: Dec. 1973.	#	#	--	#	
A18	WTox 147; Report T 119: BTS 27919: Acute oral toxicity study in dogs (with histopathology). Morgan, H.E. and Turnbull, G.J.; Date: 1973/74.	#	#	--	#	

No.	STUDY	D	US	CH	FAO	*
A19	WTox 159; Report T 167: Amitraz impurity. BTS 33220: Acute oral toxicity to male boots-wistar rats. O'Donovan, M.R. and Smithson, A.; Date: Oct. 1978.	#	--	--	#	
A20	WTox 134; Report T 112: Acaricides: Dermal toxicity to rats of RD 27271 hydrochloride and RD 21103 hydrochloride. Metcalf, W.; Date: June 1970.	#	--	--	--	
A21	WTox 131; Report T 11: BTS 27271: Acute oral toxicity to rabbits. Sutton, M.M.; Date: Aug. 1972.	#	--	--	#	
A22	(quoted in I1); Report T 294: Technical Amitraz: Assessment of the delayed contact hyper-sensitivity in the guinea pig. Kynoch, S.R. and Parcell, B.I.; Date: Feb. 1988.	#	--	--	--	
A23	WTox 38; Report TX 73002 BTS 27419: Acute toxicity in baboons. Patton, D.S.G.; Date: Jan. 1973.	#	#	--	#	
A24	Report YM 72011 BTS 27419: Acute dermal toxicity to rabbits. Sutton, M. M.; Williams, P.A. Date: 1972.	--	#	--	#	
A25	BTS 27271: Acute oral toxicity study in dogs. Unpublished report -. TX 73004 from The Boots Company submitted to WHO. Morgan, H.E. Date: 1973a.	--	#	--	#	
A26	BTS 28037: Acute oral toxicity study in dogs. Unpublished report -. TX 73015 from The Boots Company submitted to WHO. Morgan, H.E. Date: 1973b	--	--	--	#	
A27	BTS 27919: Acute oral toxicity study in dogs-Histopathology. Unpublished report -. TX 74004 from The Boots Company submitted to WHO. Morgan, H.E. Date: 1974a.	--	--	--	#	
A28	BTS 28369: Acute oral toxicity study in dogs-Histopathology. Unpublished report -. TX 74006 from The Boots Company submitted to WHO. Morgan, H.E. Date: 1974b.	--	--	--	#	
A29	BTS 27271: Acute oral toxicity study in dogs-Histopathology. Unpublished report -. TX 73030 from The Boots Company submitted to WHO. Morgan,H.E. and Williams, G.A.H. Date: 1973.	--	#	--	#	
A30	RD 27271: Effects on u/v erythema in guinea pigs. Unpublished report -. PM 70100 from The Boots Company submitted to WHO. Patton, D.S.G. Date: 1970.	--	--	--	#	
A31	BTS 27271: Effects in conscious dogs of small intravenous doses. Unpublished report -. TX 73017 from The Boots Company submitted to WHO. Patton, D.S.G. Date: 1973.	--	#	--	#	
A32	BTS 27419: Eye-irritancy in the rabbit. Unpublished report -. TXM 72037 from The Boots Company submitted to WHO. Sutton, M.M. and Metcalf,W. Date: 1972.	--	#	--	#	
A33	Report TX 75025: Amitraz: comparison of oral and topical administration to pigs. Morgan, H.E et al. Date: 1975	--	#	--	#	
A34	Skin Irritancy of formulation SN 6554 Containing 20% 27419. (Unpublished study including letter dated Feb. 2, 1973 from W.K.S. Moore to D.K. Lewis, received Oct. 7, 1974 under 5G1558; submitted by Upjohn Co., Kalamazoo, Mich.; CDL: 094254-Q). Moore, W.K.S. Date: 1973	--	#	--	--	
A35	Comparison of Acute Toxicities to Rats of RD 27,271, 27,419 and 21,103: PM70092 (Unpublished study received June 24, 1976 under 6F1817; submitted by Upjohn Co., Kalamazoo, Mich.; CDL: 096419-AA). Sutton,M.M. Date: 1970.	--	#	--	--	

No.	STUDY	D	US	CH	FAO	*
A36	Dermal Toxicity and Irritation Studies in Rats and Rabbits.	--	--	#	--	
A37	Report No. TXM 72061: Acute Toxicity in Rabbit. Merrymann und Sutton	--	--	#	--	
A38	Report No. 315-75: Acute Toxicity in Rabbit, Rat.	--	--	#	--	
A39	Report No. TXM 73035: Acute Toxicity in Cat. Patton	--	--	#	--	
A40	Report No. TXM 73040: Acute Toxicity in Rat. Shaw und Williams	--	--	#	--	

No.	STUDY	D	US	CH	FAO	*
B	**SUBCHRONIC TESTING**					
B1	WTox 57; Report T 24: BTS 27419: Three week dermal toxicity to rabbits. Sutton, M.M.; Date: 1973.	#	#	--	#	
B2	WTox 58; Report T 25: Subacute inhalation toxicity to the rat of BTS 27419. Berczy, Z.S. et al.; Date: Jan. 1973.	#	#	--	#	
B3	WTox 154; Report T 26: (2nd ed.) BTS 27419 metabolite: 21 days chronic oral toxicity of BTS 28369 to rats. Shaw, J.W.; Date: Nov. 1975.	#	#	--	#	
B4	WTox 21; Report T 27: BTS 27419: 90-day toxicity study in rats. Sutton, M.M. and Williams, G.A.H.; Date: 1971.	#	#	--	#	
B5	WTox 22; Report T 28: JA 119 (BTS 27419): Three months feeding study on rats. Toyoshima, S. et al.; Date: Aug. 1972.	#	--	--	#	
B6	WTox 136; Report T 34: BTS 27419: Metabolite 90-day chronic oral toxicity in rats of BTS 27271. Shaw, J.W. and Williams, G.A.H.; Date: Nov. 1975.	#	--	--	#	
B7	WTox 23; Report T 31: BTS 27419: 90-day toxicity study in dogs. Patton, D.S.G. and Williams, G.A.H.; Date: Apr. 1971	#	#	--	#	
B8	WTox 137; Report T 32: (2nd ed.) BTS 27271: Oral toxicity study in Beagle dogs (repeated dosage for 13 weeks). Chesterman, H. et al.; Date: Nov. 1973.	#	--	--	#	
B9	WTox 155; Report T 33: BTS 28369: 90-day oral toxicity study in dogs. Morgan, H.E. et al.; Date: Sept. 1974.	#	#	--	#	
B10	WTox 60; Report T 29: BTS 27419: 90-day chronic toxicity study in mice. Shaw, J.W. and Williams, G.A.H.; Date: 1974.	#	#	--	#	
B11	WTox 61; Report T 30: JA 119 (BTS 27419): Three months feeding study on mice. Toyoshima, S. et al.; Date: Aug. 1972.	#	--	--	#	
B12	WTox 59; Report T 2: Amitraz toxicity to B6C3F1 mice by dietary administration for 13 weeks. Colley, J. et. al.; Date: Apr. 1981.	#	--	--	--	
B13	WTox 44; Report BTS 38/73511 Boots 27271 oral toxicity study in Beagle dogs (repeated dosage for 13 weeks). Chesterman, H. et al.; Date: Sept. 1973.	#	--	--	#	
B14	WTox 97; Report T 60: (2nd ed.) Amitraz, BTS 27271 and Chlorphenamidine: Effects of repeated daily dosing on acute responses in dogs. Morgan; H.E. et al.; Date: Apr. 1975.	#	#	--	#	
B15	BTS 27419: 14-Day Toxicity Study in Dogs, Morgan et al. 1975	--	--	#	--	

No.	STUDY	D	US	CH	FAO	*
C	**DEVELOPMENTAL TOXICITY AND REPRODUCTIVE STUDIES**					
C1	WTox 37; Report T 50: BTS 27419: Multigeneration feeding test in rats. Sutton, M.M.; Date: Sept. 1973.	#	#	--	#	
C2	WTox 175; Report T 50 (Suppl. I): Amitraz: Multigeneration feeding tests in rats -histopathology. Lancaster, M.C. and Williams, G.A.H.; Date: Aug. 1978.	#	--	--	#	
C3	WTox 34; Report T 48: BTS 27419: Teratogenicity in the rat. Sutton, M.M.; Date: Aug. 1973.	#	#	--	#	
C4	WTox 33; Report T 47: BTS 27419: Teratogenicity in the rabbit. Sutton, M.M.; Date: Aug. 1973.	#	#	--	#	
C5	Report 86156: Technical Amitraz: Teratogenicity study in the rat. Anon. Date: Dec. 1987.	--	#	--	--	
C6	Report 86154: Technical Amitraz: Range-finding study in the pregnant rat. Anon. Date: Oct. 1987.	--	#	--	--	
C7	Report 86157: Technical Amitraz: Teratogenicity study in the rabbit. Anon. Date: Dec. 1987.	--	#	--	--	
C8	Report 86155: Technical Amitraz: Range-finding study in the pregnant rabbit. Anon. Date: Oct. 1987.	--	#	--	--	

No.	STUDY	D	US	CH	FAO	*
D	**METABOLISM TESTING**					
D1	WTox 63; Report M 5: Fate of (^{14}C)-BTS 27419 applied to rats as a single oral dose. Lewis, D.K.; Date: 1971.;	#	#	--	#	
D2	WTox 64; Report M 6: Fate of (^{14}C)-BTS 27419 administered to rats in repeated oral doses. Somerville, L.; Date: Aug. 1973.	#	#	--	#	
D3	WTox 65; Report M 7:; The fate of (^{14}C)-BTS 27419 (Amitraz) when administered to mice at 100 mg/kg as a single oral dose. Hamilton, D.Y.; Date: May 1976.	#	#	--	#	
D4	WTox 66; Report M 17: Fate of (^{14}C)-BTS 27419 when administered at 15 mg/kg to dogs as a single oral dose. Hamilton, D.Y. and Somerville, L.; Date: Feb. 1974.	#	#	--	#	
D5	WTox 31; Report M 18: The conversion of BTS 27419 to BTS 27271 in the dog stomach. Somerville, L. and Hughes, K.W.; Date: Nov. 1973.	#	#	--	#	
D6	WTox 138; Report M 19: Fate of (^{14}C)-BTS 27271 when administered to dogs as a single oral dose. Hamilton, D.Y. and Somerville, L.; Date: Dec. 1973.	#	#	--	#	
D7	WTox 139; Report M 21: Fate of (^{14}C)-BTS 27271 when administered to cats as a single oral dose. Hamilton, D.Y. and Somerville, L.; Date: Jan. 1974.	#	#	--	#	
D8	WTox 67; Report M 22:; Fate of (^{14}C)-BTS 27419 when administered to cats as a single oral dose. Somerville,L.; Date: Nov. 1973.	#	#	--	#	
D9	WTox 68; Report M 23: Metabolism of (^{14}C)-BTS 27419 in calf. Part 2. Identification of major liver metabolites. Jones, E.M.; Date: Sept. 1973.	#	--	--	#	
D10	WTox 69; Report M 46: Metabolism of (^{14}C)-BTS 27419 in calf and cow. Part I. Identification of major urinary metabolites. Jones, E.M.; Date: May 1973.	#	--	--	#	
D11	WTox 70; Report M 49: Fate of (^{14}C)-Triazid (BTS 27419) in the calf. Lewis, D.K.; Date: 1971.	#	--	--	#	
D12	WTox 72; Report M 62: Excretion and tissue residues of ^{14}C-Amitraz in a male and female baboon given a single oral dose of 10 mg ^{14}C-Amitraz per kg bodyweight. Campbell, J.K. and Needham, D.; Date: Jan. 1984.	#	#	--	--	
D13	WTox 73; Report M 63: Excretion and tissue residues of ^{14}C-Amitraz in male and female mice given a single oral dose of 10 mg ^{14}C-Amitraz/kg bodyweight. Campbell, J.K. and Needham, D.; Date: Sept. 1983.	#	#	--	--	
D14	WTox 66; Report M 66: The metabolism of ^{14}C-Amitraz by male and female rats. Campbell, J.K. and Needham, D.; Date: Jan. 1984.	#	#	--	--	
D15	WTox 71; Report M 54: Metabolism and residue studies in the calf using (^{14}C) and (^{3}H) labelled material. Anon.; Date: 1982.	#	#	--	#	
D16	WTox 74; Report M 65: A comparison of the metabolism of ^{14}C-Amitraz in rat, mouse, baboon and human. Campbell, J.K.; Date: Jan. 1984.	#	#	--	--	

No.	STUDY	D	US	CH	FAO	*
D17	WTox 77; Report M 70: Urinary excretion of (^{14}C)-Amitraz by two male humans following a single oral dose of 0,25 mg/kg bodyweight. Campbell, J.K. and Needham, D.; Date: Apr. 1984.	#	#	--	--	
D18	WTox 16; Report R 103: Estimation of BTS 28369 (Amitraz metabolite) in human urine. Hughes, K.W.; Date: Apr. 1975.	#	--	--	#	
D19	WTox 78; Report M 72:; The absorption, metabolism and excretion of Mitaban^{R} (U-36,059) in the dog from oral and dermal exposure. Hornish, R.E. and Nappier, J.M.; Date: Apr. 1983.	#	--	--	--	
D20	WTox 171; Report M 74: Identification of metabolites of Amitraz in the milk and meat of a cow dosed for 4 days with Amitraz. Phillips, M.W.A. et al.; Date: Jan. 1988.	#	--	--	--	
D21	WTox 172; Report M 75: The metabolism and distribution of Amitraz residues in the laying hen following the daily oral administration of 24,5 mg ^{14}C-Amitraz/per bird. Needham, D. and Hemmings, P.A.; Date: May 1988.	#	--	--	--	
D22	WTox 173; Report R 247 A: Amitraz technical: residues in milk and tissues of dairy cows - animal phase. Roberts, N.L. et al.; Date: March 1988.	#	--	--	--	
D23	WTox 174; Report R 266 A: Amitraz technical: residues in the eggs and tissues of the laying hen following administration by oral gavage for 28 days. Roberts, N.L. and Hakin, B.; Date: Aug. 1988.	#	--	--	--	
D24	WTox 28; Report C 71019: Fate of (^{14}C)-BTS 27419 applied to rats as a single dermal dose. Lewis, D.K.; Date: 1971.	#	#	--	#	
D25	WTox 29; Report F 73010: Metabolism of (^{14}C)-BTS 27419 in rats. Jones, E.M.; Date: Aug. 1973.	#	#	--	#	
D26	WTox 30; Report C 71014: Fate of (^{14}C)-BTS 27419 applied to dogs as a single oral dose. Lewis, D.K.; Date: 1971.	#	#	--	#	
D27	WTox 32; Report F 73019: Metabolism of (^{14}C)-BTS 27271 in dogs. Jones, E.M.; Date: Oct. 1973.	#	#	--	#	
D28	Report C 71011: Fate of (^{14}C)-BTS 27419 applied of rats as a single oral dose. Boots Hercules Agrochemicals Company Lewis, D.K.; Date: 1971.	--	#	--	--	
D29	Report AX 77010: The conversion of Amitraz to BTS 24868 dog gastric juice. Taylor, J.; Somerville, L. Date: 1977.	--	#	--	#	
D30	Report F 74001: Metabolism of (^{14}C)-BTS 27271 in dogs, part 2-identification of metabolites in the retina and choroid of the eye. Jones, E.M. Date: 1974.	--	#	--	--	
D31	Report AX 74013: Studies on the accumulation and elimination of radio-labelled residues from dogs´ eyes following oral administration of (^{14}C)-BTS 27271. Somerville, L.; Hamilton, D.Y. Date: 1974.	--	#	--	#	
D32	Report AX 74012: Fate of (^{14}C)-BTS 28369 when administered at 10 mg/kg to dogs as a single oral dose Hamilton, D.Y. and Somerville, L.; Date: 1974.	--	#	--	#	
D33	Report F 73018: Metabolism of (C14)-BTS 27419 in cats. Unpublished report -. F 73018 from The Boots Company submitted to WHO. Jones, E.M. Date: 1973	--	--	--	#	

No.	STUDY	D	US	CH	FAO	*
D34	The metabolism of FD and CRED -. I. The fate of 2,4-meta-xylidine in rats. J. Pharm. Exp. Therap. 132, 306-310. Lindstrom, H.V. Date: 1961.	--	--	--	#	
D35	Residues of amitraz and its metabolites in the plasma and tissues of calves after repeated daily dosing. Campbell, J.K. and Needham, D.; Date: 1979	--	#	--	--	
D36	The Stability of Amitraz in Animal Deit; AX 76014. (Unpublished study received April 9, 1981 under 102359; submitted by Upjohn Co., Kalamazoo; Mich.; CDL: 244833-D). Somerville, L. Date: 1976	--	#	--	--	
D37	Excretion Balance, Metabolic Fate and Tissue Residue Following Treatment of Rats with Amitraz and N-(2,4-demithy-lphenyl)-N-methylformamidine. J. Environ. Sci Health B16(5), 547-555. Knowles, Charles D. and Herman J. Benezet. Date: 1981.	--	#	--	--	
D38	Report 73011: Metabolism of (^{14}C)-BTS 27419 in calf and cow. Part II.	--	--	#	--	
D39	Dermal absorption of ^{14}C-Amitraz EC formulation by male and female pigs given a single topical application of 18 mg a.i., Campbell und Needham, 1984	--	#	#	--	

No.	STUDY	D	US	CH	FAO	*
E	**CHRONIC TESTING**					
E1	WTox 24; Report T 35: BTS 27419: Carcinogenicity and long-term study in rats. Sutton, M.M. and Offer, J.; Date: Nov. 1973.	#	#	#	#	
E2	WTox 35: BTS 27419: 80-week carcinogenicity study in mice. Final report. Burnett, R. et al.; Date: May 1976.	#	#	#	#	
E3	WTox 81; Report T 233: Amitraz: 104-week tumourgenicity study in mice. Final report. Colley, J. et al.; Date: Dec. 1983.	#	#	#	--	
E4	WTox 25; Report T 36: BTS 27419: Two-year oral toxicity study in dogs. Morgan, H.E. et al.; Date: Sept. 1973.	#	#	#	#	
E5	WTox 36:Amitraz. Further evaluation of 80-week mouse study. Unpublished report -. HGD 79002 from The Boots Company submitted to WHO. Jones, E.M. Date: 1973e.	--	#	--	#	
E6	Final Report: Carcinogenicity of chemicals present in man's environment. Contract -. NIH-NCI-E-68-311. Reported by Bio-Research consultants, submitted to WHO by The Boots Company. NCI Date: 1973.	--	--	--	#	
E7	The carcinogenicity assessment group preliminary review on oncogenicity of amitraz. Albert, R.; Date: 1977	--	#	--	--	

No.	STUDY	D	US	CH	FAO	*
F	**MUTAGENICITY**					
F1	WTox 83; Report T 51: BTS 27419, BTS 27271, BTS 27919 and BTS 28369: Mutagenicity testing in bacterial in vitro systems. Everest, R.P. and Wilcox, P.; Date: March 1976.	#	#	--	#	
F2	WTox 84; Report T 52: BTS 27419: Mutagenicity testing against Salmonella typhimurium strains TA 1535, TA 1537 and TA 1538 in the presence and absence of liver microsomes from male and female mice. Everest, R.P. and Wilcox, P.; Date: Sept. 1976.	#	--	--	#	
F3	WTox 90; Report T 93: Evaluation of Amitraz (U-36,059) and its metabolites in the Salmonella microsome test. Zimmer, D.M. et al.; Date: Sept. 1977.	#	--	--	--	
F4	WTox 91; Report T 220: Technical Amitraz: Ames bacterial mutagenicity test. McGregor, D.B. and Prentice, R.D.; Date: Nov. 1983.	#	#	--	--	
F5	WTox 140; Report T 201: Technical BTS 27271 Ames bacterial mutagenicity test (metabolite of Amitraz). Richold, M. et al.; Date: Sept. 1983.	#	#	--	--	
F6	WTox 148; Report T 202: Technical BTS 27919 Ames bacterial mutagenicity test (metabolite of Amitraz). Richold, M. et al.; Date: Sept. 1983.	#	#	--	--	
F7	WTox 160; Report T 168: Amitraz impurity. BTS 33220: In vitro bacterial mutagenicity testing. Wilcox, P.; Date: Sept. 1978.	#	#	--	--	
F8	WTox 161; Report T 169: In vitro bacterial mutagenicity testing of an Amitraz sample containing 1% BTS 33220. Everest, R.P. and Wilcox, P.; Date: May 1979.	#	#	--	#	
F9	WTox 94; Report T 227: Technical Amitraz: Mouse lymphoma mutation assay. McGregor, D.B. and Riach, C.G.; Date: Jan. 1984.	#	#	--	--	
F10	WTox 157; Report T 225: Technical BTS 24868 (2,4-Xylidine): Mouse lymphoma mutation assay. McGregor, D.B. and Riach, C.G.; Date: Nov. 1983.	#	#	--	--	
F11	WTox 85; Report T 53: BTS 27419: Mutagenicity study in the intraperitoneal host-mediated assay. Wilcox, P.; Date: Apr. 1976.	#	#	--	--	
F12	WTox 86; Report T 54: BTS 27419: Mutagenicity study in the male mouse perivisceral cavity host-mediated assay. Everest, R.P.; Date: Sept. 1976.	#	#	--	#	
F13	WTox 89; Report T 88: Evaluation of Amitraz (U-36,059) and its metabolites (U-40,481, U-36,893, U-54,915A and U-54,914) in the DNA damage/Alkaline elution assay. Petzold, G.L. et al.; Date: Sept. 1977.	#	--	--	#	
F14	WTox 93; Report T 222: Technical Amitraz: Unscheduled DNA synthesis in human embryonic cells. McGregor, D.B.and Riach, C.G.; Date: Nov. 1983.	#	#	--	--	
F15	WTox 158; Report T 235: Technical BTS 24868 (2,4-Xylidine): Induction of morphological transformation in C3H/10T 1/2 cells. Riach, C.G. et al.; Date: March 1984.	#	--	--	--	

No.	STUDY	D	US	CH	FAO	*
F16	WTox 87; Report T 55: Dominant lethal assay of Amitraz in the female mouse. Palmer, A.K. and James, P.A.; Date: Apr. 1977.	#	#	--	#	
F17	WTox 88; Report T 56: Dominant lethal assay of Amitraz in the male mouse. Palmer, A.K. and James, P.A.; Date: Apr. 1977.	#	#	--	#	
F18	WTox 156; Report T 199: A micronucleus study in mice using BTS 24868 (2,4-Dimethylaniline). Hounsell, I.A.G. and Walker, A.K.; Date: Sept. 1983.	#	--	--	--	
F19	WTox 92; Report T 221: Technical Amitraz: Induction of morphological transformation in C3H 10T 1/2 cells. McGregor, D.B. and Riach, C.G.; Date: Nov. 1983.	#	--	--	--	
F20	Amitraz. Ames-tests on a sample produced by Nissan Chemical Industries. Unpublished report -. TX 78068 from The Boots Company submitted to WHO. Tuplin, J.A. and Wilcox, A. Date: 1978.	--	--	--	#	
F21	Further mutagenicity studies on pesticides in bacterial reversion assay systems (Moriy et al.: Mutation Res. 116:185-216) Date: 1983.	--	#	--	--	

No.	STUDY	D	US	CH	FAO	*
G	**NEUROTOXICITY TESTING**					
G1	Moser, VC & MacPhail, C:Investigations of amitraz neurotoxicity in rats. III. Fundam. Appl. Toxicol., 1989, 12 (1), 12-22.	#	--	--	--	
G2	Moser, VC: Investigations of amitraz neurotoxicity in rats: IV. Fundam. Appl. Toxicol., 1991, 17(1), 7-16.	#	--	--	--	
G3	Moser, VC et al.:Rat strain and stock comparisons using a functional observational battery Toxicol. Appl. Pharmacol., 1991, 108(2), 267-283.	#	--	--	--	
G4	Gilbert, ME & Dyer, RS: Increased hippocampal excitability produced by amitraz. Neurotoxicol Teratol., 1988, 10 (3), 229-235.	#	--	--	--	
G5	Gilbert, ME & Mack, CM: Enhanced susceptibility to kindling by chlordimeform may be mediated by a local anaesthetic action. Psychopharmacol., 1989, 99(2), 163-167.	#	--	--	--	
G6	Moser, VC et al. Investigations of amitraz neurotoxicity in rats. I. Effects on operant performance. Fundam. Appl. Toxicol., 1987, 9, 131-139.	#	--	#	--	
G7	Boyes und Moser;Investigations of amitraz neurotoxicity in rats. II. Effects on visual-evoked potential. Fund. Appl. Toxicol., 1987, 9, 140-153.	#	--	#	--	

No.	STUDY	D	US	CH	FAO	*
H	**OTHER TESTING**					
H9	WTox 56; Report T 224: Animal studies on the treatment of poisoning by Amitraz (a formamidine pesticide) and Xylene. Turnbull, G.J.; Date: 1983.	#	--	--	--	
H10	WTox 96; Report T 46: BTS 27419: Effects on the oestrus cycle of the rat. Merryman, D.C. and Sutton, M.M.; Date: Feb. 1972.	#	#	--	#	
H11	WTox 55; Report T 223: Extrapolation from safety data to management of poisoning with reference to Amitraz (a formamidine pesticide) and Xylene. Bonsall, J.L. and Turnbull, G.J.; Date: 1983.	#	--	--	--	
H12	WTox 107; Report T 158: Amitraz: Investigation of effects on the thymus gland and oestrous cycle in mice. Brown, D.J. et al.; Date: May 1978.	#	#	--	#	
H13	WTox 121; Report T 238: Technical Amitraz: The effect of dietary administration on the oestrous cycle and hormones in the mouse. Hounsell, I.A. and Rush, K.C.; Date: Feb. 1984.	#	#	--	--	
H14	WTox 82; Report T 49: BTS 27419: Effect on pregnancy, parturition and care of the young in rats. Sutton, M.M.; Date: Sept. 1973.	#	#	--	#	
H15	WTox 95; Report T 241: Amitraz: Pharmacological aspects of toxicity. Turnbull, G.J.; Date: Apr. 1984.	#	--	--	--	
H16	WTox 123; Report M 71: The effect of Amitraz on the hepatic mixed-function oxidase system of male and female mice following oral administration. Needham, D.; Date: March 1984.	#	--	--	--	
H17	WTox 124; Report T 67: Anticholinesterase activity of RD 27419, a prominent acaricide, and some derivatives. Lewis, D.K.; Date: May 1970.	#	--	--	--	
H18	WTox 12; Report without number: Observations on man. Anon.; Date: without.	#	--	--	--	
H19	WTox 98; Report T 64: BTS 27419 - Effects in conscious dogs of small intravenous doses. Parkinson, R. et al.; Date: 1971.	#	#	--	#	
H20	WTox 99; Report T 65: Effects of the acaricide BTS 27419 and the related sulphur analogues BTS 30559 and BTS 30561 on the cardiovascular system of the cat, particularly the ear vascular bed. Parkinson, R. et al.; Date: Oct. 1971.	#	#	--	#	
H21	WTox 100; Report T 66: BTS 27419: Effects on thermoregulation in mice. Sutton, M.M.; Date: 1972.	#	#	--	#	
H22	WTox 101; Report T 68: The effects of BTS 27271, BTS 27419 and BTS 21103 (Chlordimeform) on the central actions of reserpine in the mouse and rat. Parkinson, R.; Date: 1974.	#	#	--	#	
H23	WTox 102; Report T 69: The effects of BTS 27271, BTS 27419 and BTS 21103 (Chlordimeform) on the pressor responses to tyramine in the pithed rat. Parkinson, R.; Date: 1974.	#	#	--	#	

No.	STUDY	D	US	CH	FAO	*
H24	WTox 105; Report T 109: The diuretic action of the acaricides RD 27271 and RD 27419 in mice. Sim, M.F.; Date: Dec. 1970.	#	--	--	#	
H25	WTox 108; Report T 159: A comparison of the hypothermic effects of Amitraz (BTS 27419) in male and female CFLP mice. Berry, P.A.; Date: Nov. 1976.	#	#	--	#	
H26	WTox 109; Report T 160: Some pharmacological effects of the acaricide RD 27271 and related compounds. Parkinson, R. and Sim, M.F.; Date: Oct. 1970.	#	--	--	--	
H27	WTox 110; Report T 206: Experimental studies of drug-induced impaction colic in the horse. Roberts, M.C. and Seawright, A.A.; Date: 1983.	#	--	--	--	
H28	WTox 111; Report T 212: Inhibition of monoamine oxidase by the pesticide Chlordimeform and related compounds. Aziz, S.A. and Knowles, C.O.; Date: 1973.	#	--	--	--	
H29	WTox 112; Report T 215: Formamidine Pesticides - Metabolic aspects of neurotoxicity. Benezet, H.J. et al.; Date: 1978.	#	--	--	--	
H30	WTox 113; Report T 216: Interaction of formamidines with the platelet 5-Hydroxytryptamine uptake system. Johnson, T.L. and Knowles, C.O.; Date: 1982.	#	--	--	--	
H31	WTox 114; Report T 218: Increased feeding in rats treated with Chlordimeform and related formamidines: A new class of appetite stimulants. Pfister, W.R. et al.; Date: 1978.	#	--	--	--	
H32	WTox 115; Report T 228: Formamidine induced feeding and behavioural alteration in the rat. (abstr.) Pfister, W.R. and Yim, G.K.W.; Date: 1977.	#	--	--	--	
H33	WTox 116; Report T 229: Inhibition of rat brain monoamine oxidase by insecticides, acaricides and related compounds. Kadir, H.A. and Knowles, C.O.; Date: 1981.	#	--	--	--	
H34	WTox 117; Report T 230: Prostaglandin synthesis inhibited by formamidine pesticides. Yim, G.K.W. et al.; Date: 1978.	#	--	--	--	
H35	WTox 118; Report T 231: Inhibition of mammalian monoamine oxidase by two formamidine pesticides. Rieger, J.A. et al.; Date: 1980.	#	--	--	--	
H36	WTox 119; Report T 232: Inhibition of rat brain monoamine oxidase by formamidines and related compounds. Benezet, H.J. and Knowles, C.O.; Date: 1976.	#	--	--	--	
H37	WTox 120; Report T 234: Effect of Amitraz on contractions of the guinea-pig ileum in vitro. Pass, M.A. and Seawright, A.A.; Date: 1982.	#	--	--	--	
H38	WTox 122; Report T 242: Effects of Amitraz on the cardiovascular and respiratory systems in the dog. (abstr.) Cullen, L.K. and Reynoldson, J.A.; Date: 1983.	#	--	--	--	
H39	Report -. P 72622: Effects of BTS 27149 and BTS 27271 on the responses of rabbit ear blood vessels to catecholamines and antidromic stimulation. Unpublished report -. P 72622 from The Boots Company submitted to WHO. Anonymous. Date: 1972	--	--	--	#	

No.	STUDY	D	US	CH	FAO	*
H40	Report SS 78001: Amitraz. Investigation of effects on the thymus gland and oestrus cycle in mice - statistical analysis of vaginal smear data and thymus weights. Unpublished report -. SS 78001 from The Boots Company submitted to WHO. Channon, E.J. and Cryer, P.C. Date: 1978.	--	#	--	#	
H41	Report P 75030: BTS 27271: an attempt to produce and quantify the flushing response in the pig. Unpublished report -. P 75030 from The Boots Company submitted to WHO. Parkinson, R. Date: 1975.	--	--	--	#	
H42	Report PM 71022: The effects of BTS 27419 on Trafuril-induced erythema on the guinea-pig. Unpublished report -. PM 71022 from The Boots Company submitted to WHO. Parkinson, R. and Yates, D.B. Date: 1971.	--	--	--	#	
H43	Amitraz: The effect of dietary administration on the oestrous cycle and hormones in the mouse. Hounsell, I.A. and Rush, K.C.; Date: 1984.	--	#	--	--	
H44	Evaluation of Experimental Use Permit Pesticides: Report on Upjohn's Compound U36059 for Pear Psylla Control in Michigan. (Michigan, Dept. of Public Health, unpublished study; CDL: 96415-U) Bloomer, A.W. Date: 1975	--	#	--	--	
H45	U-36059: Safety Evaluation of Baam (R) 1.5 EC in Dogs Following a Single Topical Exposure: 527-9610-TJK-76. (Unpublished study received June 24, 1976 under 6F1817; submitted by Upjohn Co., Kalamazoo, Mich.; CDL: 096415-K) Kakuk, T.J.; Weddon, T.E. Date: 1976	--	#	--	--	
H46	Upjohn Report 527-9760-83-001: The Absorption, Metabolism and Excretion of Mitaban (U-36059) in Dog for Oral and Dermal Exposure. Nappier, J.M. and Hornish, R.E. Date: 1983	--	#	--	--	
H47	Investigations of amitraz neurotoxicity in rats. I. Effects on operant performance. Moser, VC et al.; Fundam. Appli. Toxicol., 1987, 9, 131-139	#	--	#	--	
H48	Investigations of amitraz neurotoxicity in rats. II. Effects on visual-evoked potential. Boyes und Moser; Fund. Appl. Toxicol., 1987, 9, 140-153	#	--	#	--	

No.	STUDY	D	US	CH	FAO	*
MH	**MEDICAL DATA**					
MH1	WTox 14; Report T 82: A human pharmacology study involving dermal application of BTS 27419. Hall, J.E.; Date: March 1971.	#	--	--	--	
MH2	WTox 15; Report T 83: A study of the effects of oral administration of a metabolite (BTS 27271) of Amitraz to volunteers. Hall,J.E. et al; Date: May 1975.	#	#	--	#	
MH3	WTox 13; Report T 85: BTS 27419: Clinical observations of laboratory staff during development. Moore, W.K.S.; Date: Feb. 1972.	#	--	--	#	
MH4	WTox 153; Report R 115: The analysis of BTS 28369 in the urine of Amitraz production workers. Shirley, D.B.; Date: Dec. 1975.	#	--	--	#	
MH5	WTox 152; Report R 114: The analysis of BTS 28369 in the urine of 3 Amitraz production workers over a period of 3 weeks. Shirley,D.B.; Date: Jan. 1976.	#	--	--	#	
MH6	WTox 17; Report R 58: Investigation of BTS 27419 levels on field operator protective clothing worn during BTS 27419 spray trials. Goodall, E. and Hughes, K.W.; Date: Aug. 1974.	#	--	--	--	
MH7	WTox 18; Report R 102: BTS 28369 levels in urine of field operators engaged in a BTS 27419 spray trial. Hughes, K.W.; Date: Apr. 1975.	#	#	--	--	
MH8	WTox 19; Report T 84: Medical report on a patient who ingested Mitac (Edrizar) in Italy in 1977. Groppi, L.; Date: Oct. 1977.	#	--	--	--	
MH9	Report MS 71004: Human pharmacology study on BTS 27419. Unpublished report -. MS 71004 from The Boots Company submitted to WHO. Anonymous. Date: 1971b.	--	#	--	--	
MH10	Report: TOX/91033; Report of a double blind tolerance study of Amitraz in six adult healthy volunteers.	--	--	#	--	

No.	STUDY	D	US	CH	FAO	*
I	**EVALUATION**					
I1	Conclusions and toxicological limit values for the active ingredient Amitraz. Horne, S.D.; Date: without.	#	--	--	--	
I2	WTox 39; Report AGD 77013 (AR/DKL/SLL/258): Amitraz (BTS 27419) Discussion of the data relating to the setting of maximum permissible residue. Anon.; Date: Sept. 1977.	#	--	--	--	
I3	WTox 163; Report S 9: Amitraz: Submission to the joint meeting of the FAO panel of experts on pesticide residues in food and the environment and the WHO expert group on pesticide residues. Thomas, B. and Stenning, G.M.; Date: May 1984.	#	--	--	#	
I4	WTox 162; Report REG/47/85: Mitac^{R} (Active ingredient: Amitraz) Summary and appraisal of safety studies. Turnbull, G.J. and Somerville, L.; Date: Sept. 1985.	#	--	--	--	
I5	WTox 181; Schlußfolgerungen und toxikologische Grenzwerte für Amitraz und Mitac. Horne, S.D. and Münks, K.-W.; Date: Sept. 1991.	#	--	--	--	

Appendix 5. Further publications on toxicology of the active ingredient reviewed by the lead country (Germany)

Auer, DE.; Illness in horses following spraying with amitraz. Aust. Vet. J., 1984, 61 (8), 257-259.

Bonsall, JL & Turnbull, GJ.; Extrapolation from safety data to management of poisoning with reference to amitraz (a formamidine pesticide) and xylene. Human Toxicol., 1983, 2, 587-592.

Boyes, WK & Dyer, RS.; Comparison of amitraz and chlordimeform effects on hooded rat visual evoked potentials. Neurotoxicol., 1984, 5 (4), 76.

Boyes, WK & Moser, VC; Investigations of amitraz neurotoxicity in rats. II. Effects on visual evoked potentials. Fund. Appl. Toxicol., 1987, 9, 140-153.

Costa, LG et al.; Alpha2-adrenoceptors as a target for formamidine pesticides; in vitro and in vivo studies in mice. Toxicol. Appl. Pharmacol., 1988. 93 (2), 319-328.

Costa, LG et al.; Acute and chronic effects of the pesticide amitraz on alpha2-adrenoceptors in the mouse brain. Toxicol. Lett., 1989, 47 (2), 135-144.

Costa, LG et al.; Formamidine pesticides and alpha2-adrenoceptors studies with amitraz and chlordimeform in rats and development of a radioreceptor binding assay. Neurotoxicol. Teratol., 1989, 11 (4), 405-411.

Costa, LG et al.; The formamidine pesticides chlordimeform and amitraz decrease hepatic glutathione in mice through an interaction with alpha2-adrenoceptors. J. Toxicol. Environ. Health, 1991, 33(3), 349-358.

Crofton, KM et al.; The effects of amitraz (AMZ) administration on locomotor activity and the acoustic startle response; dosage and time dependent effects in the rat. Toxicologist, 1987, 7 (1), 254.

Crofton, KM et al.; Acute effects of amitraz on the acoustic startle response and motor activity. Pestic. Sci., 1989, 27, 1-11.

Cullen, LK & Reynoldson, JA; Effects of amitraz on the cardiovascular and respiratory systems in the dog. 22nd World Veterinary Congress Abstracts Booklet, 1983, 41.

Cullen, LK & Reynoldson, JA; Cardiovascular and respiratory effects of the acaricide amitraz. J. Vet. Pharmacol. Ther., 1987, 10 (2), 123-143.

Cullen, LK & Reynoldson, JA; Cardiovascular responses to amitraz in the presence of autonomic antagonists and agonists. Arch. Int. Pharmacodyn. Ther., 1988, 296, 45-56.

ECETOC; (European Chemical Industry Ecology and Toxicology Centre) Monograph No. 4. Hepatocarcinogenesis in laboratory rodents: Relevance in man. 1982

Folz, SD et al.; Amitraz: a tick and flea repellent and tick detachment drug. J. Vet. Pharmacol. Ther., 1986, 9, 150-156.

Frolov, BA ; Toxicity of amitraz for fowls and its acaricidal and insecticidal properties. IN: Tokoikologiya i zashchita su'skokhozyaistvennykh zhivotnykh ot ektoparazitov, Ed. V.S. Yarnykh, Moscow, USSR, 1981, 68-74.

Ghali, GZ; The metabolic basis for the acute and chronic toxicity of formamidine pesticides. Diss. Abstr. Int. B, 1981, 42 (1), 57.

Gilbert, ME; Formamidine pesticides enhance susceptibility to kindled seizures in amygdala and hippocampus of the rat. Neurotoxicol. Teratol., 1988, 10(3), 221-227.

Gilbert, ME & Dyer, RS ; Increased hippocampal excitability produced by amitraz. Neurotoxicol Teratol., 1988, 10 (3), 229-235.

Gilbert, ME & Mack, CM; Enhanced susceptibility to kindling by chlordimeform may be mediated by a local anaesthetic action. Psychopharmacol., 1989, 99(2), 163-167.

Grilli, S et al.; In vivo unwinding fluorimetric assay as evidence of the damage induced by Fenarimol and DNOC in rat liver DNA. J. Toxicol. Environ. Health, 1991, 34(4), 485-494.

Gunaratnam, P et al.; A study of amitraz toxicity in cats. Aust. Vet. J., 1983, 60 (9), 278-279.

Hsu, WH; Amitraz-induced inhibition of insulin release (hamsters). Crisp Data Base National Institutes of Health, 1991.

Hsu, WH; Effect of amitraz and chlordimeform on heart rate and pupil diameter in rats: Mediated by alpha2-adrenoceptors. Toxicol. Appl. Pharmacol., 1984, 73, 411-415.

Hsu, WH et al.; Effect of amitraz on heart rate and aortic blood pressure in conscious dogs: Influence of atropine, prazosin, tolazoline and yohimbine. Toxicol. Appl. Pharmacol., 1986, 84, 418-422.

Hsu, WH et al.; Further evidence to support the alphasub 2-adrenergic nature of amitraz-induced decrease in intestinal motility. Arch. Int. Pharmacodyn. Ther., 1987, 286(1), 145-151.

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Hsu, WH & Lu, ZX; Amitraz-induced delay of gastro-intestinal transit in mice: mediated by alpha2-adrenergic receptors. Drug Dev. Res., 1984, 4, (6), 655-660.

Hsu, WH & McNeel, SV; Amitraz-induced bradycardia and prolongation of gastroduodenal transit in dogs and their antagonism by yohimbine. Abstracts of papers presented at the 65th Annual Meeting of the conference of Research Workers in Animal Disease, 12-13 Nov. 1984, 1984, 44.

Hsu, WH & Schaffer, DD; Effects of topical application of amitraz on plasma glucose and insulin concentrations in dogs. Am. J. Vet. Res., 1988, 49 (1), 130-131.

Kimmel, EC et al.; Formamidine insecticides and chloro-acetanicide herbicides: disubstituted anilines and nitrosobenzenes as mammalian metabolites and bacterial mutagens. J. Agric. Food Chem., 1986, 34, 157-161.

Litovitz, TL et al.; 1987 annual report of the American Association of poison control centres national data collection system. Am. J. Emerg. Med., 1988, 6 (5), 479-515.

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Moser, VC et al.; Investigations of amitraz neurotoxicity in rats. I. Effects on operant performance. Fundam. Appl. Toxicol., 1987, 9, 131-139.

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Moser, VC & MacPhail, RC; Differential effects of formamidine pesticides on multiple fixed-interval responding in rats. Soc. Neurosci. Abstr., 1984, 10 (2), 1071.

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Mutsaers, CW & Van Der Velden, MA; Two cases of colon impaction in ponies, probably resulting from treatment with Taktic^{R}. Tijdschr. Diergeneeska., 1988, 113 (22), 1246-1248.

Nutrition Foundation; The relevance of mouse liver hepatoma to human carcinogenic risk. 1983.

Olibet, G et al.; In vitro and in vivo effects of formamidine pesticides and alpha2-adrenoceptors in mouse brain. Pharmacologist, 1987, 29 (3), 124.

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Oomen, PA; A sequential scheme for evaluating the hazard of pesticides to bees. Med. Fac. Landbouw. Rijks. Gent, 1986, 51 (36), 1205-13.

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Patetta, A & Manino, A; Studies on the action on honeybees of chemicals proposed for Varroa. Apic. Mod., 1986, 77 (6), 251-256.

Petney, TN & Knight, MM; The treatment of ticks on tortoises using amitraz. J. S. Afr. Vet. Assoc., 1988, 59 (4), 206.

Pronczuk, J et al.; Clinical cholinergic presentation of acute amitraz poisoning. Toxicologia, 1 (1).

Roberts, MC; Development of a drug-induced impaction colic model in the horse (amitraz). Proc. Equine Colic Res. Symp. 1982, 88-94.

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Schaffer, DD et al.; The effects of yohimbine, tolazoline, atropine, prazosin and naloxone on amitraz-induced depression of shuttle-avoidance responses in dogs. Abstr. Pap. Conf. Res., Workers in Animal Dis., 1985, 66, 14.

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Smith, BE et al.; Amitraz-induced glucose intolerance in rats: Antagonism by Yohimbine but not by Prazosin. Arch. Toxicol., 1990, 64(8), 680-683.

Tudek, B et al.; Screening for genotoxic activity of amitraz with short-term bacterial assays. Mutat. Res., 1988, 204 (4), 585-591.

WHO; (World Health Organisation) Pesticide residues in food, report of the 1973 joint FAO/WHO meeting, technical report series, 545, 1974, 13-14

Witherell, PC & Elton, WH; Evaluation of several possible treatments to control varroa mite Varroa jacobsoni (oud) on honey bees in packages. Am. Bee J., 1988, 128 (6), 441-445.

ANNEX 2

PHASE 3 REPORT

ON

DIAZINON

Lead Country: Switzerland

Contents

PART 1: TOXICITY

Mammalian acute toxicity

1.1 Introduction

Countries participating:

- Australia
- Canada
- Finland
- Great Britain
- Sweden
- United States

1.2 Types of data reviews

With the exception of the Swedish review, which is written in Swedish, all the others are written in English.

The Australian, Finnish and Swedish reviews cover all mammalian toxicology studies.

The British review covers all studies on diazinon, from mammalian toxicology to physical-chemical properties and other areas.

The Canadian review is composed of small reviews of acute toxicity, subchronic toxicity, etc.

The US review goes into greater detail and sometimes covers individual studies. The US review also discusses the acceptability or non-acceptability of the studies (i.e. compliance with EPA requirements), and for the recent studies, compliance with GLP.

The Australian, British and US reviews provide a detailed view of diazinon, including comments about the quality of the study (mainly when it is old).

The Finnish and British reviews contain summaries of the reviews or part of the reviews.

1.3 Comparison of values/results in the data reviews

See attached tables (Tables 1, 2 and 3) on acute toxicology.

With 82 references, the number of citations would have to be 492, if all the countries had evaluated the same data; but the number of citations of the references is only 153, with the following distribution: see Table 4, "Number of Citations of Acute Toxicity Studies of Diazinon".

If a reference is cited by various countries, the cited endpoints are the same. Some authorities prefer to give separated endpoints according to the sex of the animal, and others prefer to give both, the mixed value and the separated ones.

A very important fact about diazinon is the presence of decomposition products[1] that are much more toxic than the parent, namely sulfoTEPP and monothioTEPP; on this subject only Australia, Finland, Sweden and Great Britain have made evaluations, but only Australia presents a convincing set of values of the acute toxicity of these compounds.

For those countries discussing the decomposition products of diazinon, a general conclusion is that decomposed or non stabilized diazinon is much more hazardous than stabilized diazinon.

[1] Switzerland has provided in this sense an article with analytical methodology for the recognition of the decomposition products.

PART 2: ECOTOXICITY

Fish acute toxicity and avian acute and dietary toxicity

2.1 Introduction

Countries participating:

- Finland
- Great Britain
- Netherlands
- United States

2.2 Types of data reviews

In this part the Finnish reviews are written in Finnish; then only the references and values could be read.

The British reviews cover all study areas, from mammalian toxicology to physical-chemical properties and other areas.

The US reviews go into some detail and sometimes cover individual studies.

The Dutch reviews describe the conditions of experimentation and refer to uses and/or the calculation methodology.

2.3 Comparison of values/results in the data reviews

See attached tables (Tables 5, 7 and 8) on fish acute toxicology and avian acute and dietary toxicology.

For this part, only the studies concerning technical diazinon were taken into account in this comparison of reviews, and not those for the formulations.

With 10 references in the fish acute toxicology, the number of citations would have to be 40, if the four countries had evaluated the same data; but the number of citations of the references is only 13, with a distribution shown on Table 6, "Number of Citations of Fish Acute Toxicity Studies of Diazinon".

With 19 references in the avian acute and dietary toxicity, the number of citations would have to be 76, if the four countries had evaluated the same data; but the number of citations of the references is only 27, with a distribution shown on Table 9, "Number of Citations of Avian Acute and Dietary Toxicity Studies of Diazinon".

PART 3: Recommendations

It seems at this stage that the differences of quality of the reviews, as it is concluded from the various tables, is such that a potential sharing of reviews looks to be in its very early infancy. Let's give one more example: the references of companies in the British evaluation are so obscure, that the only possibility to know them is by comparing the values and the abbreviated reference with those of the other reviews.

If the idea is to share reviews, let's share from the beginning a detailed list of references; then it would be possible to share/work out the reviews.

Appendices

Table 1. Acute Toxicity of Technical Diazinon

Ref.	Study type	Endpoint	Australia	Canada	Finland	Sweden	UK	US
1	Acute oral rat	LD_{50}(mg/kg)	100-150				100-150	100-150
2			250-285		250-285		250-285	
3			215-466					
4			850	850				
5			499-775				499-775	499-775
6			300					
7			422		423	423	423	
8			614-731				696	
9			870-1031		870-1031		1012	
10			870-878					
14					76-108	76-106		76-108
15						250-408		
16								882-968
1	Acute oral mouse		82				82	82
11			187	187	187	187	187	
?							163-173	
12	Acute oral rabbit		520	520	520	520	520	
13	Acute oral dog		> 5000		> 5000			

Ref.	Study type	Endpoint	Australia	Canada	Finland	Sweden	UK	US
17	Acute dermal rat	LD_{50}(mg/kg)	> 2150	> 2150	> 2150	> 2150	> 2150	> 2150
2			455-900				455-900	455-900
18	Acute dermal rabbit		> 2000	> 2000			> 2000	> 2000
19			> 3500	3500	3500	3500	3500	
20			960					
28	Acute dermal mouse					2750		
21	Acute intraperitoneal mouse		150		159	159		
22	Acute intraperitoneal rat		260		260	260	260	
23	Acute inhalation mouse	LC_{50}(mg/m^3)	1600		1600	1600	1600	
24	Acute inhalation rat		5273 (1h)					
25			3500	3500	3500	3500	3500	3500
?							3100	
?							> 23000 (1h)	
26			> 4873					
34								9360 (unaccep.)
27	Acute inhalation guinea pig		5500		5500	5500		

Ref.	Study type	Endpoint	Australia	Canada	Finland	Sweden	UK	US
29	Eye irritation rabbit		slight		slight		slight	
30			slight	slight				
?							slight	
?							slight	
35								slight
31	Dermal irritation rabbit		non-irritant		non-irritant		non-irritant	
32			non-irritant	non-irritant				non-irritant
36								non-irritant
?							non-irritant	
?							non-irritant	
33	Dermal sensitization guinea pig		non-sensitizing		non-sensitizing		non-sensitizing	
37								non-Sensitizing
?							sensitizing	

Table 2. Acute Toxicity of Technical Diazinon (MG 8) and Formulations

Ref.	Study type	Endpoint	Australia Formulations	Canada Formulations	Finland Formulations	Sweden Formulations	UK Formulations	US Technical MG 8
38	Acute oral rat	LD_{50}(mg/kg)						1250
39			842-973					
40			> 5000					
41			1207					
1			264					
42			293-408					
43				1053				
44				1540				
45				224-442				
46				> 21000				
47				> 5000				
48				3360	3360		3360	
49				6640				
51							2000	
53							> 5000	
61							1185	
39	Acute oral mouse		517-635					
50				2800	2800		2800	
52							740	

Ref.	Study type	Endpoint	Australia Formulations	Canada Formulations	Finland Formulations	Sweden Formulations	UK Formulations	US Technical MG 8
54	Acute dermal rat	LD_{50}(mg/kg)	> 4000					
57					> 2150		> 2150	
58							> 2150	
59							> 2150	
60							> 2150	
55	Acute dermal rabbit		2559					
39			> 1250					
62								> 2020
56	Acute dermal dog		> 100					
63	Acute inhalation rat							> 2330
64					828			

Ref.	Study type	Endpoint	Australia Formulations	Canada Formulations	Finland Formulations	Sweden Formulations	UK Formulations	US Technical MG 8
65	Eye irritation rabbit		slight					
66			moderate					
69				minimally				
72					slight		slight	
73							slight	
75								minimally
67	Dermal irritation rabbit		slight					
66			moderate					
70				non-irritant				
71					non-irritant		non-irritant	
74							slight	
76								slight
68	Dermal sensitization guinea pig		non-sensitizing					
77								non-sensitizing

Table 3. Acute Toxicity of Diazinon Decomposition Products and Metabolites

Ref.	Study type	Endpoint	Australia Formulations	Canada Formulations	Finland Formulations	Sweden Formulations	UK Formulations	US Technical MG 8
78	Acute oral rat	LD_{50}(mg/kg)	10 (sulfoTEPP)					
81					5 (sulfoTEPP)			
82						5 (sulfoTEPP)		
80			2700 (metabolite III)					
80			> 5000 (metabolite V)					
79			1 (monothioTEPP)					
?								
82						1.2-2 (TEPP)	1 (monoTEPP)	
78	Acute oral mouse		25 (sulfoTEPP)					
78	Acute oral rat		65 (sulfoTEPP)					
78	Acute inhalation rat	LC_{50}(mg/m^3)	50 (sulfoTEPP)					

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Table 4. Number of Citations of Acute Toxicity Studies of Diazinon

References cited once	51
References cited twice	8
References cited three times	13
References cited four times	5
References cited five times	3
References cited six times	2

Table 5. Acute Fish Toxicity of Technical Diazinon

Ref.	Study type: Fish acute tox	Endpoint	Finland	Great Britain	Netherlands	US
Coldwater species						
1f	Salmo gairdnerii	LC_{50} (96h) (mg/l)	2.6		2.7	
2f				1.35		
7f					3.4	
9f						0.09
10f						0.4
9f	Lake trout					0.602
9f	Cutthrout trout					1.700
Warmwater species						
1f	Carassius carassius		7.6		6.4	
7f					22.7	
1f	Ictalurus ameiurus		2.7			
1f	Lepomis macrochirus		16		11.7	
2f				0.12		
5f				0.12	0.13	
8f					0.53	
5f					1.12	
5f					8.50	
8f					0.17	
5f					31.0	
10f						0.136
9f						0.168
11f						0.460
1f	Lebistes reticulatus		4		4.5	
2f	Pimephales promelas			10.3		
8f					3.70	
8f					5.6-10	
3f	Ophiocephalas punctatus			0.455		
4f	Saccobranchus fossilis			2.27		
6f	Brachydanis verio			2.12		1.400
12f	Ciprinodon variegatus					
3f	Channa punctatus				0.46	
1f	Ictalurus punctatus				2.3	
6f		LC_{50} (24h) (mg/l)		2.3		

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Table 6. Number of Citations of Acute Fish Toxicity Studies of Diazinon

References cited once	7
References cited twice	3

Table 7. Avian Acute Toxicity of Technical Diazinon

Ref.	Study type	Endpoint	Finland	Great Britain	Netherlands	US
5e	Acute oral Bobwhite quail	LD_{50} (mg/kg)		10		10
8e			5.2			5.2
9e			4.3			
10e						50
1e	Acute oral japanese quail		4	4		
4e				4.22		
2e	Acute oral Japanese quail 5d old		1.1	1.1		
11e	Acute oral Peking duck 5d old		1.9			
3e	Acute oral Pecking duck		2.7	2.7		
4e	Acute oral starling			110 - 316		
6e	Acute oral sparrow					7.5
6e	Acute oral blackbird			2.0		3.2
7e	Acute oral goslings			2.75		
12e	Acute oral Canada geese					6.16
13e	Acute oral Mallard duck					3.54
18e					3.5	
13e	Acute oral pheasant					4.33
19e					4.3	

Table 8. Avian Dietary Toxicity of Technical Diazinon

Ref.	Study type	Endpoint	Finland	Great Britain	Netherlands	US
14e	Avian dietary bobwhite quail	LC_{50} (ppm)				245
17e				245		
18e					245	
10e	Avian dietary japanese quail					167
16e			900	900		
17e				47		47
14e	Avian dietary Mallard duck					191
17e				191		
14e	avian dietary pheasant					244
17e				244		

Table 9. Number of Citations of Avian Acute and Dietary Toxicity Studies of Diazinon

References cited once	11
References cited twice	8

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ANNEX 3

PHASE 3 REPORT

ON

DICOFOL

Lead Country: Denmark

Contents

1 Introduction

This report was prepared by COWIconsult, on behalf of the Danish Environmental Protection Agency. It comprises a comparison of data reviews of dicofol done by the following countries/organizations:

- Denmark
- Germany
- The Netherlands
- the United States
- the Food and Agriculture Organization (FAO)
- the World Health Organization (WHO).

The disciplines and the study categories covered by the different countries/organisations are shown in Tables 1, 2 and 3.

Table 1. Disciplines Covered by the Different Countries/Organizations

Disciplines	DK	D	NL	US	FAO	WHO
Toxicology	x	x		x		x
Metabolism (animals)	x	x		x	x	x
Ecotoxicology	x	x	x	x		
Bioaccumulation	x		x	x	x	

Table 2. Study Categories for Toxicology Covered by the Different Countries/Organizations

Study categories	DK	D	NL	US	FAO	WHO
Metabolism	x	x		x	x	x
Acute toxicity	x	x		x		x
Irritation	x	x		x		x
Sensitization	x	x				x
Subchronic toxicity	x	x		x		x
Chronic toxicity/Carcinogenicity	x	x		x		x
Mutagenicity	x	x		x		x
Developmental and Reproductive toxicity	x	x		x		x

Table 3. Study Categories for Ecotoxicology Covered by the Different Countries/Organizations

Study categories	DK	D	NL	US	FAO	WHO
Avian acute oral, LD_{50}	x	x	x	x		
Avian dietary toxicity, LC_{50} - terrestrial bird (short-term)	x	x		x		
Avian dietary toxicity, LC_{50} - aquatic bird (short term)	x	x		x		
Avian reproduction test - terrestrial bird	x	x		x		
Avian reproduction test - aquatic bird		x		x		
Fish acute toxicity, LC_{50}, freshwater: warm-water species	x		x	x		
Fish acute toxicity, LC_{50}, freshwater: cold-water species	x		x	x		
Daphnia acute immobilization test	x		x	x		
Aquatic bioavailability, biomagnification, bioaccumulation	x	x	x	x	x	
Acute toxicity to honey bees, LD_{50}		x	x	x		
Earthworm, acute toxicity test	x	x	x			
Algae, growth inhibition	x	x	x			

2 Types of data reviews

2.1 Denmark

The Danish data review includes two separate reports, one concerning toxicology and one concerning ecotoxicology.

Structure

Each report has the following structure:

- Table of contents
- Summary
- Introduction (main applications of the pesticide)
- Chemical/physical data
- Exposure/metabolism
- Effects studies (tox.: 37 pages; ecotox.: 10 pages). The studies are subdivided in different test areas (e.g. acute toxicity, irritation, etc.). The studies are reviewed one by one. In addition there is a conclusion for each test area in the toxicological report.
- Overall conclusion
- Bibliography

Language

Both reports are in Danish.

Scope

The toxicology report:

The description of each study in the toxicology report includes methods, results and comments. These are further specified in Table 4.

Table 4. Specification of Scope and Comprehensiveness of the Danish Data Review on Toxicology

Method	Specification of guideline (OECD) Test substance and purity Animals (species, number) Dose levels Examinations
Results	Toxicological evaluations
Conclusion/comments	Evaluation of the study (acceptance/refusal) Indication of endpoint value Specification of substance related findings

The ecotoxicology report:

The description of each study in the ecotoxicology report includes methods, results and comments. These are further specified in Table 5.

Table 5. Specification of Scope and Comprehensiveness of the Danish Data Review on Ecotoxicology

Method	Specification of guideline (EPA, OECD) Test substance and purity Dose levels/concentrations Test design parameters (species, test conditions, duration etc.)
Results	Endpoint value Other observations
Conclusion/comments	Deviations from guidelines (major/minor) Overall evaluation of the study (acceptance/refusal) Evaluation of the results

2.2 Germany

The German data review consists of one report including both toxicology and ecotoxicology.

Structure

The report has the following structure:

Toxicology:

- Review of studies (17 pages). The studies are subdivided in different test areas. The studies are described briefly. The studies are in general reviewed one by one.
- Evaluation
- Classification and labelling of the substance.

Ecotoxicology:

- Review of studies (9 pages). The studies are subdivided into different test areas. For some of the test areas a risk assessment is attached. The studies are described briefly. The studies are not consequently reviewed one by one. The studies are not always possible to identify.

Bibliography

Language

The toxicology section of the report is written in English; the ecotoxicology section is written in German.

Scope

The toxicology section:

In the toxicology section each study is described briefly - in free text. The description includes the following:

- Test substance
- Animals (species, number)
- Dose levels
- Examinations (only in some cases)
- Toxicological findings related to the test substance
- Endpoint values.

The ecotoxicology section:

In the ecotoxicology section each study is likewise described briefly - in free text. The description includes the following:

- Test substance and purity
- Doses/concentrations
- Test design parameters (species, test conditions, duration etc.)
- Endpoint value
- Conclusion.

The first part of the ecotoxicological section does not have citations. Thus, only in a few cases it was possible to guess the origin of the stated values.

2.3 The Netherlands

The Dutch data review covers ecotoxicology only.

Structure

The report has the following structure:

- Summary
- Physical chemistry
- Fate
- Review of the studies (19 pages). The studies are subdivided in test areas/subjects. The studies are not reviewed one by one.
- Overall conclusion
- Bibliography.

Language

The summary, the reviews and the bibliography are in English, translated from Dutch for the purpose of this pilot project. The overall conclusion is in Dutch.

Scope

The studies are subdivided into test areas/subjects. Each test area includes a description of the studies (free text) and results (presented in tables). These are further specified in Table 6.

Table 6. Specification of Scope and Comprehensiveness of the Dutch Data Review on Ecotoxicology

Description of the studies (free text)	Test substance Dose levels/concentrations Test design parameters (species, test conditions, duration etc.) Results (conclusion of the tests, other observations, reference number)
Results (Table)	Species Test duration Endpoint value Reference number

2.4 United States

The US data review includes several separate papers, each reviewing the toxicity of dicofol in a certain test area (e.g. acute toxicity, effects on aquatic organisms, etc.). In addition, it includes two reports of an earlier date, one on toxicology and one on ecotoxicology, concerning the toxicity of the product Kelthane.

Scope

The toxicology section:

Each paper concerning toxicology includes:

- Data evaluation records, which are detailed descriptions of each study in the test area (the number of records in one paper varies from one to several). The scope and comprehensiveness of each data evaluation record is further described in Table 7.

- Reviewer evaluation.

Table 7. Specification of Scope and Comprehensiveness of Each Evaluation Record on Toxicology

Summary	Guideline (EPA) Summary of the study Acceptance of study
Materials	Test substance and purity Animals (species)
Study design	Animals (number) Dose levels Test material formulation, administration and analysis Observations Statistical analysis
Results	Toxicological findings
Discussion/Conclusion	Toxicological evaluation Endpoint value

The ecotoxicology section:

Each paper concerning ecotoxicology includes:

- Data evaluation records, which are detailed descriptions of each study in the test area (the number of records in one paper varies from one to several). The scope and comprehensiveness of each data evaluation record is further described in Table 8.

- Reviewer evaluation.

Table 8. Specification of Scope and Comprehensiveness of Each Evaluation Record on Ecotoxicology

Summary	Test material Study type Study citation Conclusion Recommendation Background
Materials and methods	Test animals Test system Dose Design Statistics
Reported results	Endpoints Values
Study author's conclusion	Conclusions Quality assurance measures (guideline, GLP)
Reviewers discussion	Test parameters Statistical analysis Discussion Results Adequacy of study

Language

The review is written in English.

2.5 WHO

The data review from WHO covers toxicology only.

Structure

The report has the following structure:

- Review of studies (20 pages). The studies are subdivided into different test areas (e.g. acute toxicity, irritation, etc.). The studies are reviewed one by one.
- Overall conclusion
- Toxicological evaluation (statement of ADI-humans)
- Bibliography.

Language

The review is written in English.

Procedure

Each study is described briefly - in free text. The description includes the following:

- Test substance and purity
- Animals (species, number)
- Dose levels
- Examinations
- Toxicological findings related to the test substance
- Endpoint values.

2.6 FAO

The data review from FAO concerns application patterns, residues in plants, and fate of residues in plants, animals and the environment. Subjects of relevance to this project are fate of residues in animals which are described briefly - in free text. No repeated structures are used for the descriptions.

Language

The review is written in English.

2.7 Comparison of reviews

Among countries providing a tight review structure are Denmark and the Netherlands. In the Danish reports, the description of method, results and comments is given for all studies, and each report is introduced by a summary and ended with a conclusion.

In the Dutch report, the description of method and results is likewise given for each study. The report ended with a conclusion in Dutch. A separate summary in English is available.

The presentation of the studies in the German review varies from a few lines up to a page, including descriptions, results and discussion.

WHO and FAO do not use a set format. Each study is covered in the text, where both the description and the results are presented.

The US review is generally very complex. It contains old review reports with varying structures concerning the description of each study. In addition a large number of separate papers, each comprising either reviews of newer studies or upgradings of older studies, are attached and included in the review. There is no single document or bibliography covering all studies reviewed. The citations in the old review reports are not always clear.

None of the contributors reported changing their reviews for the purpose of this project.

Terminology, ecotoxicology

Only the US review reports values in parts per million (ppm). All other reviews report values as mg/kg or the like. The Dutch review uses the term LC_0 where other countries report the same results as NOEL. The US review also reports results as MATC, a term not seen in other reviews.

Terminology, toxicology

All reviews, comprising toxicology, reports values in parts per million (ppm) and/or as mg/kg bdw.

Methodology

Tables 9 and 10 summarizes the data review methodologies as applied by the contributors to the pilot project.

Table 9. Comparison of Methodology for the Review on Toxicology

	DK	**D**	**US**	**WHO**
Conclusion or summary included?	Yes	Yes	No	Yes
Referring to GLP?	No	No	No	No
Referring to guidelines?	Yes, OECD	No	Yes, EPA	No
Are studies that do not follow testing criteria accepted and included in the data review?	Yes, if only minor deviations	-	No	-
Review language	Danish	English	English	English
Conclusion or summary language	Danish	English	English	English

NL and FAO are not included in the table as they have not reviewed any toxicological studies.
"-": not relevant.

Table 10. Comparison of Methodology for the Review on Ecotoxicology

	DK	D	NL	US	FAO	WHO
Conclusion or summary included?	Yes	No	Yes	Yes, covering an early review	No	-
Reference to GLP?	No	No	No	Yes	No	-
Reference to guidelines?	Yes, mainly OECD	No	No	Yes, US EPA	No	-
Are studies that do not follow testing criteria accepted and included in the data review?	Yes, if deviations are negligible	-	-	No	-	-
Review language	Danish	German	English (*)	English	English	-
Conclusion or summary language	Danish	-	English and Dutch	English	-	-

"-": not relevant
(*): translated especially for the purpose of this study

3 Comparison of values and results reported in the data reviews

The data reviews of dicofol have all been examined thoroughly in order to develop a comprehensive bibliography that includes all studies reviewed by all six contributors. Upon completion of the bibliography, study type, endpoint, value of result and relevant comments were compiled for all reviewed studies. The full bibliography is attached in chapter seven, and tables listing reference number (in agreement with the bibliography) and the compiled data are presented in sections 4.1 and 4.2, separated into the categories "toxicological studies" and "ecotoxicological studies".

3.1 Toxicological studies

The types of study, endpoints and results of the reviewed toxicological studies are listed in Table 11.

All studies mentioned in the bibliographies of the data reviews are listed in the bibliography presented in chapter seven. Some of these studies are not actually cited in the data reviews, and they have therefore been omitted from Table 11 and the analysis and discussion that follow. These studies have the reference numbers 2, 4, 14, 30, 31, 37, 40, 42, 43, 46, 48, 57, 68, 70, 74, 75, 91, and 95 in the bibliography.

Only study types specified in the guidance to the phase 3 reports of the OECD pilot project have been included. Especially studies regarding neurotoxicity and human toxicity have been omitted on that account.

In Table 11, the results are primarily presented by the exact endpoint and value given in the data review. If an endpoint was not stated in the data review, the phrase "no endpoint is stated" was included in the table.

Reading instruction for Table 11:

The studies are arranged according to test areas in the following order:

- Acute toxicity
- Irritation
- Sensitization
- Subchronic toxicity
- Developmental and reproductive toxicity
- Metabolism testing
- Chronic toxicity/Carcinogenicity
- Mutagenicity

Each study (reference number) can be mentioned more than once in case the contributors have evaluated the same study differently (e.g. different endpoints, different endpoint values, etc.).

Table 11. Reference No., Study Type, Endpoint, Value of Result and Comments for Studies Referred to in the Data Reviews.

The Contributors Referring to Each Study are Marked by a "1"

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
5	Acute Toxicity	LD_{50} (dermal), rabbits	> 3.0 g/kg					1		
10	Acute Toxicity	LD_{50} (dermal), rats	Males: > 5000 mg/kg bdw		1					
10	Acute Toxicity	LD_{50} (dermal), rats	Both sexes: > 5000 mg/kg bdw							1
10	Acute Toxicity	LD_{50} (dermal), rabbits	Females: > 2500 mg/kg bdw							1
11	Acute Toxicity	LD_{50} (oral), rats	Females: 500-5000 mg/kg bdw	Study is not accepted as the reviewer is uncertain on the conclusion	1					
11	Acute Toxicity	LD_{50} (oral), rats	Females: 587 mg/kg bdw	Study is not accepted as the reviewer is uncertain on the conclusion						1
12	Acute Toxicity	LD_{50} (oral), rats	Males: 500-5000 mg/kg bdw		1					
12	Acute Toxicity	LD_{50} (oral), rats	Males: 595 mg/kg bdw							1
16	Acute Toxicity	LD_{50} (oral), rats	Male rats: 1495 mg/kg bdw			1		1		1
16	Acute Toxicity	LD_{50}, rats (i.p.)	Male rats: 1150 mg/kg bdw			1				
32	Acute Toxicity	LC_{50} (4 hours), rats	Both sexes: > 5,0 mg a.i./l		1					1
41	Acute Toxicity	LD_{50} (i.p), rats	Both sexes: 1115 mg/kg bdw		1					
41	Acute Toxicity	LD_{50} (i.p), rats	Both sexes: 1115-1150 mg/kg bdw							1
45	Acute Toxicity	LD_{50} (dermal), rabbits	2.100 mg/kg					1		
49	Acute Toxicity	LD_{50} (oral), rabbits	Males: 1810 mg/kg bdw			1		1		
50	Acute Toxicity	LD_{50} (oral), rats	Males: 970 mg/kg bdw					1		
55	Acute Toxicity	LD_{50} (oral), rats	Males: 595 mg/kg bdw Females: 578 mg/kg bdw	Probably a summary of /11/ and /12/.		1				
55	Acute Toxicity	LD_{50} (dermal), rats	> 5,000 mg/kg bdw	Probably a summary of /10/		1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
55	Acute Toxicity	LC_{50}, rats	> 5.0 mg/l.	Probably a summary of /32/		1				
59	Acute Toxicity	LD_{50} (i.v.), cats	Males: < 20 mg/kg bdw							1
62	Acute Toxicity	LD_{50} (oral), dogs	Both sexes: > 4,000 mg/kg bdw			1				
63	Acute Toxicity	LD_{50} (dermal), rabbits	2,100 mg/kg bdw	The study is not accepted because of methodical short-coming	1					
63	Acute Toxicity	LD_{50} (dermal), rabbits	Males: 2,100 mg/kg bdw			1				
69	Acute Toxicity	LC_{50} (6 hours), rats	> 2.0 mg of 25% dust Kelthane/l (no deaths were reported).	Preliminary study for chronic inhalation studies.				1		
73	Acute Toxicity	LD_{50} (oral), mice	Males: 669 mg/kg bdw. Females: 675 mg/kg bdw							1
76	Acute Toxicity	LC_{50} (4 hour), rats	> 4.2 mg/l					1		
84	Acute Toxicity	LD_{50} (oral), rats	Male: 809 mg/kg bdw. Female: 684 mg/kg bdw			1		1		1
84	Acute Toxicity	LD_{50} (oral), rabbits	Males: 1810 mg/kg bdw	Probably a summary of /49/						1
84	Acute Toxicity	LD_{50} (oral), dogs	Both sexes: > 4.000 mg/kg bdw	Probably a summary of /62/						1
84	Acute Toxicity	LD_{50} (dermal), rabbits	Males: 2,100 mg/kg bdw	Probably a summary of /63/				1		
93	Acute Toxicity	LD_{50} (oral), rats	1.52 g/kg bdw					1		
6	Irritation	Eye irritation (Corneal opacity), rabbits	Kelthane formulations (end-use Kelthane) are considered corrosive to eyes (Corneal damage in some rabbits (unwashed eyes) persisted for seven days).					1		
7	Irritation	Skin irritation, rabbits: Average score for erythema and edema ∘ Eye irritation: Average score for cornea opacity, iris damage, conjunctivae (redness), conjunctivae (chemosis)	The substance is irritating to skin: Erythema: 2.25 Edema: 2.33 The substance is not irritating to eyes: Cornea opacity: 0 Iris damage: 0 Conjunc.(redn.): 1.5 Conjunc.(chem.): 1.3		1					
7	Irritation	Skin and eye irritation, rabbits	The substance is irritating to skin, but not to eyes.							1

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
21	Irritation	Skin and eye irritation, rabbits. Primary irritation score after 4 hours (skin). Corneal exposure.	Kelthane produced moderate irritation to skin (primary irritation score = 4) and to eye.			1				
56	Irritation	Skin and eye irritation, rabbits	Kelthane produced a moderate degree of irritation to both skin and eyes.			1				
9	Sensitization (Buehler Test)	Skin sensitization, guinea pigs. Evaluation of skin reaction 24 and 48 hours after challenge	The substance is found to be a sensitizer (30% of the test animals had positive reaction).		1					
9	Sensitization (Buehler Test)	Sensitization, guinea pigs	The substance is found to be a sensitizer.							1
13	Sensitization	Sensitization, guinea pigs (Erythema was scored 24 and 48 hours after challenge)	Kelthane MF417 produced hypersensitivity. Test not specified.			1				
1	Subchronic Toxicity	No endpoint is stated		Study on rats.		1				
3	Subchronic Toxicity	No endpoint is stated		Study on mice.		1				
8	Subchronic Toxicity	NOAEL (dermal tox.), rabbits	4.1 mg/kg bdw							1
8	Subchronic Toxicity	NOEL, LOEL, dermal, rabbits	NOEL: 4.1 mg/kg/day LOEL: 10.2 mg/kg/day					1		
38	Subchronic Toxicity	NOEL/NOAEL, oral, rats	1 ppm, equal to 0.07 mg/kg bdw (males) and 0.08 mg/kg bdw (females)		1	1				1
39	Subchronic Toxicity	NOEL, oral, mice	10 ppm equal to 1.6 mg/kg bdw (males) and 2.1 mg/kg bdw (females)		1					1
55	Subchronic Toxicity	NOEL, oral, dog	10 ppm equal to 0.29 mg/kg bdw			1				
55	Subchronic toxicity	NOEL, oral, mice	10 ppm equal to 2.1 mg/kg bdw			1				
47	Subchronic Toxicity	NOEL, oral, rats	20 ppm					1		
61	Subchronic Toxicity	NOAEL, dermal, rats	4 mg/kg bdw							1
66	Subchronic Toxicity	Maximum NOEL, oral, rats	20 ppm			1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
67	Subchronic Toxicity	Minimum effect level, oral, rats	20 ppm			1				
69	Subchronic Toxicity	Rats, inhalation No endpoint is stated.	Dose level: 0.012 mg/l of 25% dust formulation of Kelthane.					1		
78	Subchronic Toxicity	NOAEL, oral, mice	NOAEL not identified (< 250 ppm (lowest dose) equivalent to < 36 mg/kg bdw)	Liver changes were observed at all dose levels.						1
79	Subchronic Toxicity	NOEL, oral, rats	1 mg/kg bdw			1				
82	Subchronic Toxicity	NOEL, oral, dogs	10 ppm, equal to 0.29 mg/kg bdw (males) and 0.31 mg/kg bdw (females)		1					
82	Subchronic Toxicity	NOAEL, oral, dogs	10 ppm, equal to 0.29 mg/kg bdw							1
92	Subchronic Toxicity	NOAEL, oral, dogs	30 ppm, equal to 0.82 mg/kg bdw							1
97	Subchronic Toxicity	NOAEL, oral, rats	Not identified (< 20 ppm (lowest dose level) equivalent to 2.5 mg/kg bdw).	Body weight adversely affected at all dose levels.						1
15	Developmental and Reproductive Toxicity	NOEL, rats	100 ppm/day	Dose levels: 0; 25; 75; 100; 500 or 1000 ppm/day of Kelthane (tech.)				1		
17	Developmental and Reproductive Toxicity	NOEL (general and reproductive), rats	25 ppm			1				
18	Developmental and Reproductive Toxicity	Mice No endpoint is stated	Dose levels: 0, 7, 25, 100, 225 and 500 ppm/day of Kelthane (tech.) in the diet.			1				
18	Developmental and Reproductive Toxicity	NOEL, mice	100 ppm/day	Dicofol levels: 0, 7, 25, 100, 225 and 500 ppm/day in the diet.				1		
19	Developmental and Reproductive Toxicity	Rats No endpoint is stated	Dose levels: 0, 100, 500 or 1,000 ppm/day of Kelthane (tech.) in the diet.			1				
53	Developmental and Reproductive Toxicity	Rats: NOEL, dams, NOEL, fetuses	Dams: 2.5 mg/kg bdw Fetuses: 25 mg/kg bdw		1					
53	Developmental and Reproductive Toxicity	Rats: NOAEL, maternal toxicity ∘ NOAEL, teratogenicity ∘ NOAEL, embryofetal toxicity	Maternal tox: 0.25 mg/kg bdw Teratogenicity: 25 mg/kg bdw Embryo-fetal tox: 25 mg/kg bdw							1

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
53	Developmental and Reproductive Toxicity	Rats: Maternal NOEL and LOEL ∘ Developmental NOEL and LOEL	Maternal NOEL and LOEL: 0.25 and 2.5 mg/kg/day, respectively. Developmental NOEL and LOEL: > 25 mg/kg/day.					1		
54	Developmental and Reproductive Toxicity	Rabbits: NOEL, dams ∘ NOEL, fetuses	Dams: 0.4 mg/kg bdw Fetuses: 40 mg/kg bdw		1					
54	Developmental and Reproductive Toxicity	Rabbits: NOAEL, maternal toxicity ∘ NOAEL, teratogenicity ∘ NOAEL, embryofetal toxicity	Maternal tox: 0.4 mg/kg bdw Teratogenicity: 40 mg/kg bdw Embryo fetal tox: 4 mg/kg bdw							1
54	Developmental and Reproductive Toxicity	Rabbits: Maternal NOEL and LOEL ∘ Developmental NOEL and LOEL ∘ NOEL, fetuses	Maternal NOEL and LOEL: 4.0 and 40.0 mg/kg/day, respectively. Developmental NOEL and LOEL: 4.0 and 40.0 mg/kg/day, respectively.					1		
56	Developmental and Reproductive Toxicity	No endpoint is stated	Summary of a teratogenicity study on rats. No effects were observed at any of the dose levels (0; 5 or 25 mg/kg bdw/day).			1				
86	Developmental and Reproductive Toxicity	Rats: NOAEL (reproductive parameters) ∘ NOAEL (parental toxicity)	NOAEL (rep. param): 25 ppm, equal to 2.1 mg/kg bdw NOAEL (par. tox.): 5 ppm, equal to 0.5 mg/kg bdw							1
86	Developmental and Reproductive Toxicity	Rats: NOEL (reproduction) ∘ NOEL (general toxicity)	NOEL (repr.): 25 ppm NOEL (gen. tox.): 5 ppm			1				
86	Developmental and reproductive Toxicity	Rats: Systemic NOEL and LOEL. ∘ Reproductive NOEL and LOEL.	Systemic NOEL and LOEL: 5 and 25 ppm, respectively Reproductive NOEL and LOEL: 5 and 25 ppm, respectively.					1		
16	Metabolism Testing	Metabolism	Metabolite DCBP and DCBH were detected. Single or repeated application. Metabolite DCBP was quantified in blood. DCBH was detected but not quantified.							1
16	Metabolism Testing	It is not possible to establish any endpoint related to this record.	Single application.			1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
16	Metabolism Testing	Absorption, distribution, metabolism	Single application (i.p. dose of 230 mg Kelthane/kg). Peak concentration levels were reached in blood, kidney, lungs, heart, brain, testis, muscles and liver in 32-40 hours. Kelthane levels in fat were still increasing after 96 h. Metabolites detected in all tissues except brain: DCB and DDE.					1		
20	Metabolism Testing	Metabolism of a dicofol impurity	DDE, DDT, and alpha-chloro-DDT impurities may account for the small amounts of DDE in tissues. The latter impurity has been shown to be converted to DDE in rat liver microsomes and mouse liver in vivo.							1
24	Metabolism Testing	Distribution, metabolism, goats	% of total ^{14}C: Milk: 1.0-3.0% Fat: 7.2-15% Muscle: < 1.0-3.4% Kidney: < 1.0%; Liver: < 1.0-1.2% Urine: 3.3-13%; Faeces: 23-67%. The major metabolites were: FW-152, DCBP and DCBH.						1	
25	Metabolism Testing	Excretion, distribution, metabolism, hens	Repeated application. 51-75% of the administered ^{14}C were found in excreta. Percentage of the administered ^{14}C in eggs, tissues or organs were: 0.7-7.1% in whole eggs, 0.7-6.1% in fat, 0.2-0.5 % in muscle, 0.2-0.3 % in kidney and 0.8-0.9 % in liver. Dicofol was extensively metabolized to FW-152, DCBP and DCBH.						1	
26	Metabolism Testing	Distribution, metabolism, hens	Metabolites: FW-152, DCBP and DCBH. Distribution of dicofol and metabolites in whole egg, fat, muscle, kidney and liver are stated.						1	
27	Metabolism Testing	Elimination, metabolism, goats	Repeated application. The primary elimination route was faecal excretion, which accounted for 23-67% of the administered ^{14}C after 1-7 day depuration. Detected metabolites: FW-152, DCBH and DCBP. Fat contained the highest percentage of the administered dose, with muscles being the next largest dose.						1	

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
28	Metabolism Testing	Absorption and excretion in female rats (p,p'-dicofol and o,p'-dicofol)	Single application. p,p'-dicofol: 61% in faeces, 18% in the urine and 22% in tissues after 10 days. o,p'-dicofol: 78% in faeces, 21% in the urine and 1% in tissues after 10 days.		1					
28	Metabolism Testing	Absorption and excretion in female rats (p,p'-dicofol and o,p'-dicofol)	Single application. The two isomers showed similar distribution and excretion patterns. Both isomers were primarily excreted in faeces. Elimination half-lives were estimated to be 1.5-4 days for o,p'-dicofol and 4-7 days for p,p'-dicofol.							1
29	Metabolism Testing	Absorption and excretion in male rabbits	Examined at three dose levels (0.04; 4 and 61 mg/kg). 0.04 mg/kg: 62% in faeces, 27% in the urine, 11% in tissues and 1% in the blood after 14 days. 4 mg/kg: 12% in faeces, 16% in the urine, 2% in tissues and 0,04% in the blood after 14 days. 61 mg/kg: 17% in faeces, 12% in the urine, 3% in tissues and 0,04% in the blood.		1					
33	Metabolism Testing	Gap junctional intercellular communication, rats	Repeated application. Dicofol (1,000 ppm) enhanced the development of gamma-glutamyltrans-peptidase-positive hepatic foci in nitrosamine-initiated Sprague-Dawley rats.							1
38	Metabolism Testing	Tissue residue pattern for dicofol in tissues, rats	The tissue residue pattern for dicofol in liver, gonad and fat was dose-related in both sexes.			1				
44	Metabolism Testing	Accumulation, rats	Repeated application. Dose levels: 1, 3.2, 10 or 32 ppm Kelthane/day for 8 weeks. Kelthane accumulated in the body fat during feeding. Cessation of feeding led to gradual elimination. Two weeks after cessation of feeding 75% of the accumulated Kelthane had disappeared from the body fat of females. Eight weeks after cessation of feeding 90% of the accumulated Kelthane had disappeared from the body fat of both males and females.					1		

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
51	Metabolism Testing	Effect on adrenal cortisteroid synthesis, rats	The serum corticosterone level was significantly decreased at 500 and 1500 ppm.			1				
60	Metabolism Testing	Absorption, distribution, excretion, mice	Single application. 60% of the administered dose was eliminated within 4 days primarily in faeces. Peak tissue concentrations were reached within 24-48 h. Highest concentrations in adipose tissue followed by liver, kidney, lung, heart, blood plasma, brain, whole blood and spleen.							1
64	Metabolism Testing	Effects on adrenal cortical synthesis, dogs	Dicofol had a negative effect on the adrenal cortical synthesis.			1				
68	Metabolism Testing	It is not possible to establish any endpoint relating to this record.				1				
71	Metabolism Testing	hepatic mixed-function oxidase (MFO) inducing effect of dicofol, rats	Dicofol concentrations of 10 ppm and above increased MFO activity.							1
80	Metabolism Testing	Tissue residues, hens	Repeated application. Dose levels: 0.5; 1.5 and 5 ppm. Schematic outline.						1	
81	Metabolism Testing	Tissue residues, cows	Repeated application. Dose levels of 0; 10; 30 or 1100 ppm. Schematic outline.						1	
87	Metabolism Testing	Absorption, distribution and excretion ◦ Average half-life (tissues), T½, rats	Males: 101 % in faeces, 20% in the urine and 2% in tissues after 8 days. Females: 57% in faeces, 42% in the urine and 2% in tissues after 8 days. T½: Males: 31,5 h; Females: 30,0 h		1					
87	Metabolism Testing	Absorption, distribution and excretion ◦ Average half-life (tissues), T½, rats	Dicofol was eliminated mainly in faeces. Essentially all of the dose was excreted within 8 days. Highest concentrations were found in adipose tissue ad adrenal gland. Females had higher tissue levels than males. Elimination half-life were estimated to be 30 h (Male: 31.5 h, Female: 30.0 h)							1

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
87	Metabolism Testing	It is not possible to establish any endpoint related to this record, rats	Single application.			1				
88	Metabolism Testing	Absorption and excretion, female rats	Repeated application. 58% in faeces, 17% in the urine and 0,7% in tissues after 32 days.		1					
88	Metabolism Testing	Absorption and excretion, female rats	Repeated application. 75% of the administered dose was excreted within 16 days., and mainly in faeces. Elimination half-life was estimated to be 6-14 days.							1
88	Metabolism Testing	T½ (from tissues and in excreta). It is not possible to establish any other endpoints related to this record, rats	Repeated application. T½ = 2 weeks.			1				
89	Metabolism Testing	Hepatic mixed -function oxidase (MFO) inducing effect, mice	Repeated application. MFO activity was increased 22-43% in females (at 14.9 mg/kg bdw and above) but unaffected in males.							1
90	Metabolism Testing	Liver mixed func-tion oxidase (MFO) inducing effect, mice	Repeated application. Dicofol increased MFO activity in male mice at 250 and 800 ppm.							1
94	Metabolism Testing	Metabolism, rats	The following metabolites were identified: p,p'-isomers of DCBH, DCBP, FW-152, OH-DCBP, OH-DCBH, DCBA, DBA-glycine, CHA and CBA. FW-152 was the most common metabolite, especially in liver and faeces.						1	
94	Metabolism Testing	Absorption, excretion and metabolism, rats	Single application. Males: 62% in faeces, 16% in the urine, 4% in tissues and 0.1% in blood after 7 days. Females: 32% in faeces, 19% in the urine, 23% in tissues and 0.3% in blood after 7 days. Identified metabolites: p,p'-isomers of DCBH, DCBP, FW-152, OH-DCBP, OH-DCBH, DCBA, DBA-glycine, CHA and CBA.		1					

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
94	Metabolism Testing	Absorption and excretion, rats	Single dose application. Males and females excreted 78% and 51%, respectively, of the dose in 7 days. Faecal and urine excretion accounted for 32-61% and 16-19%, respectively. Tissue concentrations were much higher in females than males.							1
94	Metabolism Testing	It is not possible to establish any endpoint related to this record.	Single application.			1				
94	Metabolism Testing	Distribution, metabolism, elimination, rats	Single dose application. Faeces was the major route of excretion. Fat contained the highest concentration of residues in organs and tissues. The following metabolites were detected: DCBH, DCBP, FW-152, hydroxy-DCBP, DCBA and the glycine of DCBA.						1	
94	Metabolism Testing	Absorption, metabolism and excretion, rats	Single application. Faeces was the major route of excretion (males: 61.7% and females: 32.2% after 168 h). 15% was excreted in urine for both sexes after 168 h. Highest residue level were observed in adipose tissue at 48 h: 200 ppm, or 30.6% of dose in males and 547 ppm or 80.5% of dose in females. The major pathway of dicofol includes the following metabolites: FW-152, DCBP, DCBA, DCBH, CBA, CHA and various hydroxy or conjugated secondary metabolites.					1		
96	Metabolism Testing	Distribution, cows	Repeated application (17 days of dosing and 34 days of observation). Maximum level of kelthane of 0,55 ppm in the milk was reached after 6 days of exposure (in the diet).		1					
3	Carcinogenicity	No endpoint is stated.	Dicofol is found to cause hepato cellular carcinoma in male mice at doses of 264 and 528 ppm/day. A similar effect was not found in female mice or in rats (both sexes).		1	1		1		1
22	Carcinogenicity	No endpoint is stated	Examination of selected liver sections from long term study in mice. There is found no evidence for a carcinogenic effect of dicofol in male mice at doses of 264 and 528 ppm/day.		1					

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
22	Carcinogenicity	No endpoint is stated	Examination of selected liver sections from long term study in mice. Dicofol were found to produce a dose related increase in males only in the incidence of non-neoplastic simple hepatic nodules.			1				
23	Carcinogenicity	No endpoint is stated	Re-examination of selected liver sections from long term study in mice. There is found no evidence for a carcinogenic effect of Dicofol in male mice at doses of 264 and 528 ppm/day.		1					
23	Carcinogenicity	No endpoint is stated	Re-examination of selected liver sections from long term study in mice. Dicofol were found to produce a dose related increase in males only in the incidence of non-neoplastic simple hepatic nodules.			1				
51	Chronic Toxicity/ Carcinogenicity	NOEL, rats	5 ppm, equal to 0,22 mg/kg bdw (males) and 0,27 mg/kg bdw (females). No evidence on carcinogenic effect.		1					
51	Chronic Toxicity/ Carcinogenicity	NOAEL, rats	5 ppm, equal to 0.22 mg/kg bdw							1
51	Chronic Toxicity/ Carcinogenicity	NOEL, rats	5 ppm, equal to 0.22 mg/kg bdw in males and 0.27 mg/kg bdw in females.			1				
51	Chronic Toxicity/ Carcinogenicity	NOEL, LEL (chronic toxicity), rats	NOEL: 5 ppm ∘ LEL : 50 ppm					1		
65	Chronic Toxicity	No endpoint was stated	Study on dogs. No significant effects were found at doses of 100, 300 or 900 ppm.			1				
68	Chronic Toxicity	Dose levels with no treatment related changes	20 and 100 ppm.	Study in rats		1				
85	Chronic Toxicity Carcinogenicity	No endpoint is stated	Examination of selected liver sections from long term study in mice. Dicofol produced in males a dose related increase only in the incidence of non-neoplastic simple hepatic nodules.			1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
92	Chronic Toxicity	Dogs: NOEL, LOEL	NOEL: 30 ppm ∘ LOEL: 180 ppm					1		
98	Chronic Toxicity Carcinogenicity	No endpoint is stated	Examination of selected liver sections from long term study in mice. Dicofol produced in males a dose related increase only in the incidence of non-neoplastic simple hepatic nodules.			1				
99	Chronic Toxicity /Carcinogenicity	No endpoint is stated	Examination of selected liver and lung sections from long term study in mice. Dicofol produced in males a dose related increase only in the incidence of non-neoplastic simple hepatic nodules.			1				
34	Mutagenicity (DNA synthesis assay)	Mutagenic effect (yes/no). Evaluation according to OECD 482.	No		1					
34	Mutagenicity (DNA synthesis assay)	Mutagenic effect (yes/no)	No			1				1
34	Mutagenicity (DNA synthesis assay)	Mutagenic effect (yes/no)	No The study is classified as unacceptable, as no effect upon UDS in primary rat hepatocytes was noted for the test compound at any of the dose levels.					1		
35	Mutagenicity (CHO/HGPRT - gene mutation)	Mutagenic effect (yes/no)	No		1	1		1		1
36	Mutagenicity (Chromosome aberrations and sister chromatid exchange)	Mutagenic effect (yes/no)	No							1
52	Mutagenicity (Ames test)	Mutagenic effect (yes/no)			1	1				1
52	Mutagenicity (Ames test)	Mutagenic effect (yes/no)	No The study is classified as provisionally unacceptable pending submission of positive control assays without activation.					1		
58	Mutagenicity (in vitro cytogenetic assay)	Mutagenic effect (yes/no)	No		1	1		1		1
72	Mutagenicity (microbial mutagen test)	Mutagenic effect (yes/no)	No			1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
77	Mutagenicity (in vivo cytogenetic test)	Mutagenic effect (yes/no)	No		1	1				1
77	Mutagenicity (in vivo cytogenetic test)	Mutagenic effect (yes/no)	No The study was classified as unacceptable, as the MTD may not have been reached, no mitotic index data were available, and no data on females was submitted.					1		
83	Mutagenicity (microbial mutagenicity test)	Mutagenic effect (yes/no)	No Test substance was Kelthane	Test systems: S.typhimurium, E. coli, B. subtilis.						1
100	Mutagenicity (Mutagen test in Drosophila v.)	Mutagenic effect (Yes/no)	No							1

Similarity in reviewed studies

In the table below, it is shown to what extend the contributors reviewed the same studies concerning toxicology.

Table 12. Number of Studies in Different Study Categories Reviewed by the Same Contributors

Study categories	Number of studies reviewed in:					
	Total	**One country**	**Two countries**	**Three countries**	**Four countries**	**Five countries**
Metabolism	24	19	1	3	-	1
Acute toxicity	17 (*)	8	7	2	-	-
irritation	4	3	1	-	-	-
Sensitization	2	1	1	-	-	-
Subchronic toxicity	16	12	3	1	-	-
Chronic toxicity/ Carcinogenicity	10	6	2	-	2	-
Mutagenicity	9	4	-	-	5	-
Developmental and Reproductive toxicity	8	4	1	3	-	-
Total	90	57	16	9	7	1

(*) The references summarizing some of the other studies are not included.

It is evident from Table 12 that most of the studies (63%) are only reviewed by one country, 16 studies (18%) are reviewed by two countries, 9 studies (10%) are reviewed by three countries, 7 studies (8%) are reviewed by four countries and only one study (1%) is reviewed by five countries.

The reviews from Denmark (DK) and WHO refer to many identical studies, while especially the German (D) review refers to a large number of studies which are not used by other countries. However, some of these appear to be summaries of the studies used by the other contributors. FAO has only reviewed studies concerning metabolism.

There is to a large degree similarity between the reported endpoints. Table 13 summarizes the applied endpoints.

Table 13. Endpoints for Various Study Types as Applied in the Data Reviews

	DK	D	US	WHO
Acute toxicity	LD_{50} LC_{50}	LD_{50} LC_{50}	LD_{50} LC_{50}	LD_{50} LC_{50}
Irritation	eye + skin irritation	eye + skin irritation	eye + skin irritation	eye + skin irritation
Sensitization	sensitization	sensitization	sensitization	sensitization
Subchronic toxicity	NOEL	NOEL	NOEL LOEL	NOAEL
Chronic toxicity/ carcinogenicity	NOEL	NOEL	NOEL LEL LOEL	NOAEL
Mutagenicity	mutagenicity	mutagenicity	mutagenicity	mutagenicity
Developmental and reproductive toxicity	NOEL	NOEL	NOEL LOEL	NOAEL

Effect studies

The effect studies are characterized by being conducted according to standardized guidelines. All contributors use the same endpoints: LD_{50} or LC_{50} for acute toxicity and NOEL or NOAEL for subchronic toxicity, chronic toxicity/carcinogenicity, developmental and reproductive toxicity. In addition to the NOEL, the US data review applies LOEL (lowest observed effect level) and LEL (lowest effect level) as endpoints. The LOEL is always used together with NOEL.

Toxicokinetic studies

The test area concerning toxicokinetics is characterized by not following standardized guidelines. It appears from the different ways in which the contributors cite the same study and the lack of unambiguous endpoints. However, the contributors arrive at the same conclusions concerning absorption, distribution, metabolism and excretion.

Table 14. Comparison of Conclusions on Study Categories of Toxicology

Study categories	DK	D	US	WHO
Metabolism	-	-	-	-
Acute toxicity	Oral: - Dermal: - Inhal.: LC_{50}: > 5.0 mg/l	Oral: slightly toxic Dermal: slightly toxic Inhal.: non-toxic	Oral: Moderate toxicity Dermal: - Inhal.: -	Oral: moderate toxicity Dermal: LD_{50}: - Inhal.: LC_{50}: > 5.0 mg/l
Irritation	Irritating to skin but not to eyes	Moderate irritating to skin and eyes	Considered severe eye irritant (no study) No data on skin irritation	Irritating to skin but not to eyes
Sensitization	Sensitizer	Sensitizer	No data on sensitization	Sensitizer
Subchronic toxicity:	Oral: NOEL(rat): 0.07 mg/kg bdw NOEL(dog): 0.29 mg/kg bdw NOEL(mice): 2.6 mg/kg bdw	Oral: Same as DK	Oral: NOEL(rats): 20 ppm Dermal: NOEL(rabbit): 4.1 mg/kg bdw LOEL(rabbit): 10.2 mg/kg bdw	NOAEL(rat): 0.07 mg/kg bdw NOAEL(dog): 0.29 mg/kg bdw NOAEL(mice): 2.1 mg/kg bdw
Chronic toxicity/ Carcinogenicity	NOEL(general tox), rat: 0.22 mg/kg bdw No carcinogenic effect	NOEL (general tox.), dogs: 30 ppm No carcinogenic effect	Possible human carcinogen	NOAEL(general tox.), dogs: 30 ppm ≈ 0.82 mg/kg bdw No carcinogenic effect
Mutagenicity	No mutagenicity	No mutagenicity	No mutagenicity	No mutagenic effect
Developmental and Reproductive toxicity	No teratogenic effect Reproductive effect: -	No teratogenic effect Rats: NOEL (general tox.): 5 ppm NOEL (reproduct.): 25 ppm	No teratogenicity Rats: NOEL (general tox.): 5 ppm NOEL (reproduction): 25 ppm	No teratogenic effect NOEL (general tox.), rat: 5 ppm ≈ 0.5 mg/kg bdw NOEL (reproduction): 25 ppm ≈ 2.1 mg/kg bdw

Conclusions

From Table 14 it appears that there are gaps in the Danish and the US data reviews in different test areas. In the Danish review there is no information on reproductive toxicity and the acute toxicity is not evaluated, as studies on acute oral and dermal toxicity are rejected. In the US review, there is no information on acute dermal toxicity, inhalation, skin irritation and sensitization.

In general the contributors come to the same conclusion in various study categories (sensitization, subchronic toxicity, mutagenicity, reproductive toxicity and teratogenicity). Inconsistency may be observed in the study categories oral toxicity, irritation, and carcinogenicity.

Studies concerning acute oral toxicity in rats are: /11/, /12/, /16/, /49/, /50/, /55/ and /93/. Denmark reports values of LD_{50} in intervals (both sexes: 500-5000 mg/kg bdw) /11/,/12/. Denmark rejects the study as the reviewer is uncertain of the conclusion. The WHO reports the exact values of LD_{50} (males: 595 mg/kg bdw; females: 587 mg/kg bdw). From /55/, which is a summary of /11/ and /12/, Germany likewise reports the exact values of LD_{50} (the same as WHO).

Other inconsistencies among acute studies have been noted. Denmark reports exact values of LD_{50} (i.p) (1115 mg/kg bdw), while WHO reports an interval (1115-1150 mg/kg bdw) /41/. Furthermore in /10/, Denmark reports an endpoint value for males, while WHO reports the same endpoint value as valid for both sexes.

Studies /7/, /21/ and /56/ concern irritation. Based on these, Denmark and WHO come to the same conclusion that dicofol is irritating to skin, but not to eyes /7/. Germany concludes that dicofol is moderately irritating to skin and eyes /21/ and /56/, and the US concludes that dicofol is a severe eye irritant. The US conclusion is based on studies that can not be identified. It is not possible to give any explanation of the different classifications as Denmark is the only contributor who specifies the criteria for classification (EC-classification).

Studies concerning chronic toxicity/carcinogenicity are: /3/, /22/, /23/, /51/, /65/, /68/, /85/, /92/, /98/ and /99/. All the contributors report the same conclusion, that dicofol is found to cause hepatocellular carcinoma in male mice /3/. No carcinogenic effects were observed in female mice or rats. Based on the other studies, which especially concern reexamination of liver sections from the carcinogenic study, the carcinogenic effect is rejected by DK, D and WHO. There is no reference to these studies in the US review. On the basis of the findings in male mice the US classifies the substance as a possible human carcinogen (according to the EPA guideline for cancer risk assessment).

There is no inconsistency in the overall conclusion in the study category teratogenicity, but the NOEL values stated by the different countries or organizations varies within the same studies /53/, /54/. Thus for rats, Denmark reports NOEL (dams): 2.5 mg/kg bdw, while WHO and the US report NOEL (dams): 0.25 mg/kg bdw. The low NOEL is based on clinical signs of toxicity (salivation). In the Danish evaluation the salivation is not included in the criteria for the NOEL (dams).

DK and WHO report the NOEL (dams) for rabbits being 0.4 mg/kg bdw, based on histopathological findings in the liver /54/. The US report the NOEL (dams) as 4.0 mg/kg bdw, as they evaluate the biological significance of the effect in the liver as unclear.

3.2 Ecotoxicological studies

The types of study, endpoints and results of the reviewed ecotoxicological studies are listed in Table 15.

All studies mentioned in the bibliographies of the data reviews are listed in the bibliography presented in chapter seven. Some of these studies are not otherwise cited in the data reviews, and they have therefore been omitted from Table 15 and the analysis and discussion that follow. These studies have the reference numbers 105, 106, 175, 176, 177, 179, 180 and 181 in the bibliography.

Only study types specified in the guidance to phase 3 of the Pilot Project have been included. In particular, a number of studies of effects on aquatic invertebrates have been omitted on that account. These include tests with mysid shrimps, eastern oysters, fiddler crabs, stone flies and the amphipod *Hyella azteca*. An avian bioconcentration study has also been omitted.

In Table 15, the results are primarily presented by the exact endpoint and value given in the data review. If an endpoint was not stated in the data review, but the result given in a manner that enables determination of the endpoint, the endpoint has been stated in order to facilitate the comparison between the contributors' reviews.

Reading instruction for Table 15:

The studies are arranged according to test areas in the following order:

- Avian acute oral LD_{50}
- Avian dietary toxicity LC_{50} - aquatic bird
- Avian dietary toxicity LC_{50} - terrestrial bird
- Avian reproduction test - aquatic bird
- Avian reproduction test - terrestrial bird
- Fish acute toxicity LC_{50}, freshwater: warm-water species
- Fish acute toxicity LC_{50}, freshwater: cold-water species
- Daphnia acute immobilization test
- Aquatic bioavailability, biomagnification, bioaccumulation
- Acute toxicity to honey bees LD_{50}
- Earthworm, acute toxicity test
- Algae, growth inhibition.

Individual studies (reference numbers) can be mentioned more than once in case the contributors have evaluated the same study differently (e.g. different endpoints, different endpoint values, etc.)

Table 15. Reference No., Study Type, Endpoint, Value of Result and Comments for Studies Referred to in the Data Reviews.

The Contributors Referring to Each Study are Marked by a "1"

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
107	Avian Acute Oral LD_{50}	LD_{50}	> 640 mg Kelthane/kg	US: Does not fulfill guideline requirements.				1		
108	Avian Acute Oral LD_{50}	LD_{50}	Kelthane, not calculated	US: Does not fulfill guideline requirements.				1		
109	Avian Acute Oral LD_{50}	LD_{50}	265 mg/kg			1				
110	Avian Acute Oral LD_{50}	NOEL	> 640 mg formulation/kg bw/d	DK: Does not fulfill guideline requirements.	1	1				
112	Avian Acute Oral LD_{50}	LD_{50} (10d)	< 640 mg formulation/kg bw/d	DK: Does not fulfill guideline requirements.	1					
112	Avian Acute Oral LD_{50}	NOEL	> 320 mg formulation/kg bw/d			1				
112	Avian Acute Oral LD_{50}	LC_{50} (10d)	320-640 mg Kelthane AP/kg bw/d				1			
110	Avian Dietary Toxicity LC_{50} - Aquatic Bird (short-term)	LC0 (10d)	> 640 mg Kelthane AP/kg bw/d				1			
111	Avian Dietary Toxicity LC_{50} - Aquatic Bird (short-term)	LC_{50}	1651 ppm Kelthane technical					1		
113	Avian Dietary Toxicity LC_{50} - Terrestrial Bird (short-term)	LC_{50}	1237 ppm Kelthane technical	US: Does not fulfill guideline requirements.				1		
114	Avian Dietary Toxicity LC_{50} - Terrestrial Bird (short-term)	LC_{50}, Bobwhite q∘ LC_{50}, Japanese Q∘ LC_{50}, Fasanen ∘ LC_{50}, Mallard	Bobwhite Quail: 3010 mg/kg ∘ Japanese Quail: 1418 mg/kg ∘ Fasanen: 2126 mg/kg ∘ Mallard Duck: 1651 mg/kg			1				
115	Avian Dietary Toxicity LC_{50} - Terrestrial Bird (short-term)	LC_{50}	3100 ppm Kelthane technical					1		
116	Avian Dietary Toxicity LC_{50} - Terrestrial Bird (short-term)	LC_{50}	2126 ppm Kelthane technical					1		
101	Avian Reproduction Test Aquatic Bird	NOEC	0.5 mg dicofol/kg diet (18 weeks)			1				

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
101	Avian Reproduction Test - Aquatic Bird	LOEC (egg shell quality)	10 ppm diet					1		
117	Avian Reproduction Test - Aquatic Bird	NOEL ∘ NOEL	5 ppm ∘ 10 ppm	US: Does not fulfill guideline requirements.				1		
118	Avian Reproduction Test - Terrestrial Bird	Eggshell thinning	8.3-13.5% thinner shells at 10 mg/kg food in screech owls	Purity of dicofol unknown			1			
119	Avian Reproduction Test - Terrestrial Bird	LOEC (eggshell thinning)	3 µg/g diet					1		
120	Avian Reproduction Test - Terrestrial Bird	NOEC	120 mg dicofol technical/kg diet (19 weeks)	US: Does not fulfill guidelines requirements	1	1		1		
121	Avian Reproduction Test - Terrestrial Bird	LC_{50}	1545 ppm Kelthane technical	US: Does not fulfill guideline requirements.				1		
122	Avian Reproduction Test - Terrestrial Bird	LC_{50}	1746 ppm Kelthane technical	US: Does not fulfill guideline requirements.				1		
124	Avian Reproduction Test - Terrestrial Bird	Eggshell thinning	33.4 mg dicofol/kg diet (48d): 7.2% thinner shells			1				
125	Avian Reproduction Test - Terrestrial Bird	LC_{50}	> 100 ppm Kelthane technical	US: Does not fulfill guideline requirements.				1		
126	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	LC_{50}	3.6 ppm Kelthane (48h)	US: Does not fulfill guideline requirements.				1		
127	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	LC_{50}	2.3 ppm Kelthane (48h)	US: Does not fulfill guideline requirements.				1		

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
128	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	LC_{50} ∘ LC_{50}	4.6 mg Kelthane AP/l (24h) ∘ 3.6 mg Kelthane AP/l (48h)				1			
128	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	not relevant		DK: Does not fulfill guideline requirements. Test performed with old product.	1					
129	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	LC_{50}	2.95 ppm Kelthane					1		
130	Fish Acute Toxicity LC_{50}, Freshwater: Warm-water Species	LC_{50}	0.51 ppm Kelthane technical					1		
132	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50} ∘ LC_{50}	0.74 mg Kelthane AP/l (24h) ∘ 0.52 mg Kelthane AP/l (48h)				1			
133	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50} ∘ NOEC	0.37 mg a.i./l (96h) ∘ 0.025 mg a.i./l					1		
134	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}		US: Does not fulfill guidelines requirements. Results not reported.				1		
135	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species			US: Results not reported.				1		
136	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.52 ppm Kelthane (48h)	US: Does not fulfill guidelines requirements.				1		
137	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50} ∘ LC_{50}	2.3 mg Kelthane AP/l (24h) ∘ 2.3 mg Kelthane AP/l (48h)				1			
137	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	not relevant		DK: Does not fulfill guideline requirements. Test performed with old product.	1					

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
140	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	NOEL (larval length)	< 1.0 µg a.i./l					1		
141	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	MATC	> 4.4 and < 7.9 µg a.i./l					1		
142	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50} ∘ NOEC	1.1 mg a.i./l (96h) ∘ < 0.18 mg a.i./l	DK and US: Does not fulfill guidelines requirements.	1			1		
143	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50} ∘ NOEC	0.21 mg a.i./l (96h) ∘ < 0.056 mg a.i./l	DK and US: Does not fulfill guidelines requirements	1			1		
144	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species			US: Results not reported				1		
145	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species			US: Results not reported				1		
146	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.95 ppm Kelthane	US: Does not fulfill guidelines requirements.				1		
147	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.0869 ppm Kelthane technical	US: Does not fulfill guidelines requirements.				1		
148	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.0531 ppm Kelthane technical	US: Does not fulfill guideline requirements.				1		
149	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.36 ppm Kelthane technical					1		
150	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LOEL ∘ NOEL	0.039 ppm Kelthane technical ∘ 0.019 ppm Kelthane technical					1		

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
151	Fish Acute Toxicity LC_{50}, Freshwater: Cold-water Species	LC_{50}	0.50 ppm Kelthane technical					1		
152	Daphnia Acute Immobilizatio n Test	LC_{50}	0.075 mg/l (48h)	D: Citation not clear.		1	1			
153	Daphnia Acute Immobilizatio n Test	NOEC ∘ EC_{50}	1.0 mg a.i./l (24h) ∘ 4.5 mg a.i./l (24h)		1					
153	Daphnia Acute Immobilizatio n Test	NOEC EC_{50}	1.0 mg dicofol technical/l (24h) 4.5 mg dicofol technical/l (24h)				1			
155	Daphnia Acute Immobilizatio n Test	LC_{50} ∘ NOEC	0.31 mg a.i./l ∘ 0.96 mg a.i./l		1					
155	Daphnia Acute Immobilizatio n Test	EC_{50}	0.14 ppm	US: Invalid as an LC_{50}-study.				1		
160	Daphnia Acute Immobilizatio n Test	LC_{50}	0.08 mg dicofol/l (24h)	D: Citation not clear.		1	1			
102	Aquatic Bio-availability, Bio-magnification, Bio-accumulation	BCF in guppy ∘ BCF in Salvinia	54000 (4d) ∘ 11000 (4d) dicofol	Concentrations in various species, distribution of ^{14}C-dicofol			1			
103	Aquatic Bio-availability, Bio-magnification, Bio-accumulation	BCF ∘ BCF ∘ BCF	6600 (28d, muscles) ∘ 17000 (28d, organs) ∘ 25000 (BIOFAC, 122d= 90% steady state)		1					
103	Aquatic Bio-availability, Bio-magnification, Bio-accumulation	BCF ∘ Half-life	25000 (28d) ∘ 33±2.1 days dicofol						1	
103	Aquatic Bio-availability, Bio-magnification, Bio-accumulation	BCF ∘ BCF ∘ Half-life	6600 (28d, muscles) ∘ 17000 (28d, organs) ∘ 33 days dicofol					1		

Ref#	Study	Endpoint	Value	Comments	DK	D	NL	US	FAO	WHO
104	Aquatic Bio-availability, Bio-magnification, Bio-accumulation	BCF ∘ BCF ∘ BCF	10000 (28d, wo) ∘ 6600 (28d, ed) ∘ 17000 (28d, ned) p,p-dicofol	BCF in Bluegill Sunfish			1			
165	Acute Toxicity to Honey Bees LD_{50}	LD_{50}, oral	≈100 µg Kelthane/bee			1				
166	Acute Toxicity to Honey Bees LD_{50}	LD_{50} (honey bee) ∘ LD_{50} (Megachile r.)	12.20 µg/bee ∘ 78.28 µg/bee					1		
167	Acute Toxicity to Honey Bees LD_{50}	toxicity	low toxicity in all 3 test species					1		
168	Acute Toxicity to Honey Bees LD_{50}	mortality	No abnormal mortality when 1% emulsion (18.5% EC) applied into hives					1		
169	Acute Toxicity to Honey Bees LD_{50}	LD_{50} (contact)	> 50 µg dicofol/bee			1	1			
169	Acute Toxicity to Honey Bees LD_{50}	LD_{50} (contact) ∘ LD_{50} (oral)	> 50 µg/bee ∘ > 10 µg/bee					1		
171	Earthworm, Acute Toxicity Test	LC_{50} (14d)	> 708 mg dicofol technical/kg		1		1			
171	Earthworm, Acute Toxicity Test	LC_{50} (14d)	> 708 mg a.i./kg			1				
172	Algae, Growth Inhibition	EC_{50}	0.075 mg a.i./l (96h)		1					
172	Algae, Growth Inhibition	LOEC ∘ EC_{50}	0.03 mg/l (96h) ∘ 0.075 mg/l (96h)	D: Citation not clear.		1				
172	Algae, Growth Inhibition	LOEC ∘ EC_{50}	0.036 mg/l (96h) ∘ 0.087 mg/l (96h)	D: Citation not clear.		1				
172	Algae, Growth Inhibition	NOEbC ∘ EbC_{50}	< 0.05 mg dicofol technical/l (96h) ∘ 0.073 mg dicofol technical/l (96h)				1			
173	Algae, Growth Inhibition	NOErC	< 0.5 mg dicofol technical/l (120h)				1			

Similarity in reviewed studies

In general very few studies are used by more than one country. Summarizing Table 15, seven studies (101, 128, 137, 142, 143, 153, 155) are referred to by two countries and seven studies (103, 110, 112, 120, 169, 171, 172) are referred to by three or more countries. The remaining 44 studies are referred to only by one country each. Especially the US review refers to a large number of studies not used by any other country or organization.

The two predominant study types are tests with birds and fish. Among the 20 tests with birds, only one test was cited in two reviews and three tests were cited in three reviews. A similar result was found for toxicity studies with fish. Here, only two studies out of a total of 24 studies were cited in two reviews.

There is to a large degree similarity between the reported endpoints. Table 16 summarizes the applied endpoints.

Table 16. Endpoints for Various Study Types as Applied in the Data Reviews

	DK	D	NL	US	FAO	WHO
Avian, acute oral toxicity	LD_{50} NOEL	LD_{50} NOEL	LC_{50} LC_0	LD_{50}		
Avian, dietary toxicity	NOEC	LC_{50} NOEC		LC_{50} LOEC		
Avian, reproduction test	NOEC	NOEC		LC_{50} NOEL NOEC LOEC		
Fish, acute toxicity	LC_{50} NOEC	LC_{50}	LC_{50}	LC_{50} NOEL NOEC LOEL MATC		
Daphnia, acute immobilization test	LC_{50} EC_{50} NOEC	LC_{50}	LC_{50} EC_{50}	EC_{50}		
Aquatic bioavailability, biomagnification and/or bioaccumulation	BCF	BCF	BCF	BCF Half-life	BCF Half-life	
Honey bees, acute toxicity		LD_{50}	LD_{50}	LD_{50}		
Earthworm, acute toxicity	LC_{50}	LC_{50}	LC_{50}			
Algae, acute toxicity	EC_{50}	EC_{50} LOEC	EbC_{50} NOEbC NOErC			

*"**C**oncentration" or "**L**evel"*

The most frequent reason why countries report different endpoints is their application of a NOEC vs. a NOEL (or similarly LOEC or LOEL). There is no unambiguous pattern for the use of these terms.

In addition to the use of NOEC and LOEC, the US data review applies MATC as an endpoint.

Regarding the use of LC_{50} and LD_{50}, the first is applied for measurements of concentration and the latter for measurements of doses. This, however, was not the case for the data review prepared by the Netherlands. In this review, LC_{50} and LC_0 were applied in acute oral toxicity tests (avian) for test results with the unit mg/kg body weight/day.

Prefixes for biomass and growth rate

The Netherlands have in two instances specified EC_{50} and NOEC as either E_bC_{50}, NOE_bC or NOE_rC. The prefixes b and r designate the result in the algae growth inhibition test being measured as either biomass (b) or the specific growth rate (r).

Effect, no effect or low effect

It differs considerably whether the endpoints LC_{50}, LOEC or NOEC are being applied. It seems that LC_{50} (or LD_{50}) is applied when possible, and NOEC (or NOEL) is applied when no effects are observed or in addition to LC_{50} (or LD_{50}). LOEL, LOEC and MATC are only applied in the US data review.

EC_{50} is applied for sublethal test parameters. This, however, does not seem consistent for daphnia acute immobilization tests where it is not always clear whether the test parameter is immobilization or mortality.

Bioaccumulation test

Regarding the tests on bioavailability, biomagnification and bioaccumulation, the US and FAO data reviews include both the endpoints BCF and half-life. BCF, only, is applied by Denmark, Germany and the Netherlands. BCF is in some instances calculated, based on models predicting a steady state concentration, which has not been reached during the experiment. Such a result has been referred to in data reviews from Denmark, the US and FAO. In the Danish review both the calculated BCF and the BCF based directly on the results from the experiment were quoted. In the US and FAO data reviews, only the calculated BCF was quoted, but only the US data review noted that the value was based on modelling the steady state concentration.

Test duration

For one study, which was quoted in two data reviews (the Danish and the US), it was observed that the endpoint was the same, but the time duration different. In the Danish review the 48 h LC_{50} acute test with daphnia was presented, whereas the 96 h value was presented in the US review.

Active ingredient or formulated product

In the Danish review, all reported values are presented as content of active ingredient if possible. Values derived from studies using product formulations are converted for that purpose. All other contributors only report the value from the study, whether it is given as active ingredient or formulation.

Data gaps in the data reviews

The Danish, German, Dutch and US data reviews more or less cover all study categories included in the pilot project. Ecotoxicology is not included in WHO's data review, and the FAO review includes one study on bioaccumulation. Table 3 summarizes the study categories covered in the data reviews.

Conclusions

In general the six contributors have come to the same conclusions. Inconsistency may be observed between Denmark and the Netherlands, both regarding the acute immobilization test on daphnia and the algae growth inhibition test. The conclusions are summarized in Table 17.

Studies concerning the daphnia test are: /152/, /153/, /155/ and /160/. The Netherlands reports LC_{50} values of 0.075-0.08 mg/l /152/ and /160/, which are much lower than the Danish reported LC_{50} and EC_{50} values of 0.31 and 4.5 mg/l /153/, /155/. However, the Dutch conclusion notices that the studies are insufficiently documented. The Danish conclusion is also based on additional studies not included in this project (studies of toxicity in scrimps and oysters, revealing a LC_{50} value of 0.06 mg/l and a EC_{50} value of 0.0223 ppm, respectively).

Studies /172/ and /173/ concern the algae test. The Netherlands report an E_bC_{50} value of 0.073 mg/l /172/, and Denmark reports an EC_{50} value of 0.075 mg/l /172/. The Dutch conclusion describes the studies as showing some inadequacies between this value and a NOE_rC value of < 0.5 mg/l /173/, giving rise to the conclusion: "probably moderately to highly toxic to algae". The Danish conclusion is based only on the value from /172/.

Table 17. Comparison of Conclusions on Study Categories of Ecotoxicology

Study categories	DK	D	NL	US	FAO	WHO
Avian acute oral, LD_{50}	-	-	-	slightly toxic	n.i.	n.i.
Avian dietary toxicity, LC_{50} - terrestrial bird (short-term)	-	-	n.i.		n.i.	n.i.
Avian dietary toxicity, LC_{50} - aquatic bird (short term)	-	-	n.i.		n.i.	n.i.
Avian reproduction test - terrestrial bird	-	-	n.i.	-	n.i.	n.i.
Avian reproduction test - aquatic bird	-	-	n.i.	-	n.i.	n.i.
Fish acute toxicity, LC_{50}, freshwater: warmwater species	highly toxic	-	moderately to highly toxic	highly toxic	n.i.	n.i.
Fish acute toxicity, LC_{50}, freshwater: coldwater species						
Daphnia acute immobilization test	very highly toxic to crustaceans	-	moderately toxic to crustaceans	-	n.i.	n.i.
Aquatic bioavailability, biomagnification, bioaccumulation	-	-	highly accumulating	-	-	n.i.
Acute toxicity to honey bees, LD_{50}	n.i.	(*) geringe toxizitaet	slightly toxic/ not-dangerous	low toxicity	n.i.	n.i.
Earthworm, acute toxicity test	-	(*) schwach toxic	slightly toxic	n.i.	n.i.	n.i.
Algae, growth inhibition	very highly toxic	-	probably moderately to highly toxic	n.i.	n.i.	n.i.

"-": No conclusion on that category drawn by reviewer.
"n.i.": Category not included in review.
"*": German formulations both comparable to "slightly toxic".

4 Potential use of reviews

The findings of the data reviews from the four countries and from FAO and WHO have been presented and compared in the above sections of the report. This section discusses whether the data reviews prepared by Germany, the US, the Netherlands, FAO and WHO can be used by the Danish Environmental Protection Agency either to support the data reviewed by Denmark or in place of actually conducting a Danish data review. In the following, each data review is mentioned briefly.

Denmark

The Danish data review is relatively detailed, specifying methods, results and conclusions for all studies. It includes reference to the use of guideline and possible deviations, but there is no information on GLP. The review contains a separate summary and conclusion for toxicology and ecotoxicology as well as a complete bibliography.

Germany

There is a fairly small overlap of studies reviewed by both Germany and Denmark. The German review varies considerably in its form. It may be specific and detailed in some study areas and very brief in others. The data review does not include a summary on ecotoxicology, and it does not indicate whether the reviewed studies were conducted in accordance with standardized guidelines or with GLP. The German data review contains important data with no citations. The majority of these data cannot be evaluated but may be equivalent to studies in the bibliography. In general, the conclusions regarding the study areas in the German review are very close to the Danish conclusions.

The Netherlands

The Dutch review, which covers ecotoxicology only, has a structure similar to that of the Danish review. There are relatively few overlaps between studies reviewed by the Netherlands and Denmark, making a direct comparison difficult. In some instances the Netherlands and Denmark come to different conclusions regarding the selected study areas. The Dutch review does not include information about whether the reviewed studies are conducted in accordance with guidelines and GLP.

United States

The US data review is very extensive. It is, however, difficult to view as a whole, because each study is reviewed several times, and because a final update on all study areas has not been prepared. Only a small number of the studies reviewed by the US have also been reviewed by Denmark. Thus, it is not possible to decide whether the US and Denmark would reach the same conclusion when given the same data. Based on the existing material, it seems in general that the US review applies stricter criteria for accepting studies than does the Danish. Also, it seems that the US conclusions are relatively severe compared to the Danish. The US review includes information about whether the studies are conducted in accordance with guidelines (EPA) and GLP (only the ecotoxicological section).

WHO

The studies in the WHO review, all in the area of toxicology, are to a large degree the same as the studies reviewed by Denmark. The criteria for determining the value of the endpoints seem to be in accordance with the Danish criteria. WHO and Denmark also usually come to the same conclusions. The WHO data review does not contain information about test guidelines or GLP, but includes a summary.

FAO

Only a few studies reviewed by FAO fall under study areas included in the report. Based on such minor overlap of data, it is not possible to evaluate further the possibility of using the FAO data review. The FAO review does not include references to the application of standardized guidelines or GLP. Nor does it contain a summary.

Level of application

Based on the findings of the above analysis, it is not possible to suggest using another country's data review in place of actually conducting a Danish data review. However, using other countries' or organizations' data reviews as a support to the Danish review may well be desirable when the data supplied to the Danish reviewers are insufficient or of low quality.

Common criteria

In order to benefit as much as possible from using other reviews, a more standardized method of reviewing the data is needed. As a minimum, the following criteria should be met:

- unambiguous study citations and updated complete bibliography
- consistency in report structure and uniformity in scope and comprehensiveness of the descriptions of each study
- clearly stated criteria for acceptance/rejection of studies
- descriptions of deviations from applied test guideline for every study reviewed.

If the data reviews should actually replace each other, a development and agreement of criteria by all contributing countries and organizations is a prerequisite. This would include the following criteria among others:

- acceptable guidelines for each study area
- minimum requirements to the descriptions of each study
- acceptance/rejection of studies
- interpretation of test results (including statistical methods)

- setting conclusions in each category in the disciplines of toxicity, bioaccumulation, metabolism, etc.

5 Recommendations

Based on a comparison of data reviews on dicofol prepared by Denmark, Germany, the Netherlands, the US, WHO and FAO, it is concluded that the Danish Environmental Protection Agency (Danish EPA) cannot use other countries' or organizations' data reviews in place of actually conducting a Danish review. The Danish EPA may instead wish to use other reviews as a support to preparing the Danish reviews.

In order to use other countries' or organizations' data reviews, more standardized methods of reviewing are needed. Thus, a proper form for study citations, uniformity in structure and scope, explicit criteria for acceptance or rejection, and comprehensive descriptions of deviations from the applied guidelines must be ensured. If the reviewers in future should wish to actually replace each others' reviews, a number of criteria need to be developed and agreed upon by the contributing countries and organizations. These should at a minimum include selection of guidelines, definition of minimum requirements, criteria for acceptance or rejection, interpretation of test results, and final determination of conclusion in each study area.

Appendices

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ANNEX 4

PHASE 3 REPORT

ON

DINOCAP

Lead Country: Sweden

Contents

1 Introduction

Countries and authorities included in the report are:

- Australia
- Sweden
- Switzerland
- United Kingdom
- United States
- Food and Agriculture Organization (FAO)/World Health Organization (WHO).

Test areas covered by each country:

- Summary and Evaluation (sometimes separated):
  Australia, Sweden, UK, FAO/WHO

- Background:
  Australia, Sweden, FAO/WHO

- Chemical Identity, Chemical and Physical Properties:
  Australia, Sweden, UK

- Use and Application:
  UK

- Efficacy:
  UK

- Fate and Behaviour:
  UK

- Wildlife Data:
  UK

- Metabolism and Toxicokinetics/Biochemical Aspects:
  Australia, Sweden, UK, FAO/WHO

- Acute Toxicity:
  Australia, Sweden, UK, FAO/WHO

- Short-term Repeat Dose Toxicity/Subacute Toxicity:
  Australia, UK, FAO/WHO

- Skin and Eye Irritation; Skin Sensitization:
  Australia, Sweden, UK

- Subchronic Toxicity/Short-term Studies:
  Australia, Sweden, FAO/WHO

- Chronic Toxicity/Long-term Studies/Carcinogenicity Studies:
  Australia, Sweden, UK, FAO/WHO

- Reproductive Toxicity/Multigeneration Studies/Reproduction Studies:
  Australia, Sweden, UK, US, FAO/WHO

- Developmental Toxicity/Teratogenicity:
  Australia, Sweden, UK, FAO/WHO:

- Genotoxicity/Mutagenicity:
  Australia, Sweden, UK, FAO/WHO

- Special Studies:
  Australia: Ocular Toxicity, *in vitro* Studies
  Sweden: Mutagenicity, Teratogenicity and Reproductive Effects, Skin and Eye Irritation, Skin Sensitization
  UK: Caractogenic Study, Ocular Toxicity Study, Effect on Oxidative Phosphorylation
  FAO/WHO: Cataractogenicity

- Human Toxicity/Human Data/Human Exposure/Observations in Humans:
  Australia, Sweden, UK, FAO/WHO

- Appendices:
  (UK): Estimation of Spray Operator Exposure; Prediction of Spray Operator Exposure; Intake by Consumers

Focus of the report:

Acute Toxicity (including Irritation) (see Tables I-V - Appendix 1)
Developmental and Reproductive Toxicity (see Tables VI-VIII - Appendix 1)

2 Types of data reviews

2.1 Australia

- 60pp; in English

- each study is well presented; the review includes study methods, investigated parameters, study results, and NOEL values

- this review is recently written (1993) and is comprehensive and informative. It contains most of the information necessary to draw a conclusion on toxic effects. Each chapter and its studies are clearly displayed (text and summarizing tables); NOEL values for both maternal and foetal toxicity are presented in most of the studies.

- the Australian review document does not provide information on the quality of the data, whether the studies were done according to GLP, or whether they follow any testing criteria. Only occasionally a study was judged unacceptable.

- the review contains both a summary and a statement ("discussion"). However, the "Table of Contents" begins after the "Summary". A reversed order would have been preferable.

2.2 Sweden

- 31 pp; in Swedish.

- each study is well presented, comprehensive and detailed. The review includes study methods, studied parameters, and study results. Each separate study is discussed and evaluated. Each chapter also contains a concluding discussion.

- this review document is the oldest one (from 1986).

- no NOEL values are presented; however, the concluding remarks contain a clear evaluation of the separate studies.

- in the evaluation of developmental effects compound-related effects on maternal animals and offspring are discussed.

- if there is an indication on teratogenic effects, the type of terata on which the statement is based is also mentioned in the evaluation.

- this review document is the only one which takes toxicokinetics into consideration in the evaluation of the developmental effects.

- the review provides information on the quality of the data, that the studies follow the OECD Test Guidelines, and also a judgement on whether the studies are well performed and presented. However, there is no information on whether studies were done according to GLP.

- the review contains an executive summary and a statement about the pesticide.

- the review is written in Swedish, which is a disadvantage in this context, and there is no summary in English. (During recent years the Swedish pesticide reviews are written in English).

2.3 Switzerland

No review document was provided to the OECD Pesticide Project, only trade licences for Dinocap. These are considered inadequate for a judgement.

2.4 United Kingdom

- 99 pp; in English.

- no table of contents is included.

- the review contains extensive information on efficacy and fate and behaviour in the environment.

- each chapter is summarized.

- the review document contains a summary including limited conclusions about the pesticide.

- generally,the studies on Dinocap, its isomers and metabolites are well presented in text; however, there are some deficiencies:

    * the studies are not compiled in tables
    * occasionally, species, number of animals, and dose levels are omitted
    * no references are given.
    * there is no information on the quality of the data, whether the studies were done according to GLP, whether they follow any testing criteria, and no judgement on the acceptability of the studies.

2.5 United States

No review document was provided to the OECD Pilot Project, only final reports of two developmental toxicity studies and one two-generation study, and a notice announcing the EPA's intent to cancel registrations of Dinocap (Fed.Reg., February 6, 1989, 5908-5920). The statement is based on EPA's conclusions about the developmental effects of the pesticide.

- the final reports give comprehensive descriptions of the separate studies.

- NOELs and LOELs for systemic parental, reproductive, maternal and developmental toxicity are stated.

- there is information that the studies satisfy/don't satisfy a particular Guideline requirement.

- the studies are classified as core minimum/core supplementary.

2.6 FAO/WHO

- 20 pp; in English.

- no table of contents is included.

- the document contains a table of LD_{50} values but no conclusion on the acute toxicity of Dinocap (likewise concerning genotoxicity assays: only test results are presented).

- a NOAEL value based on a three-generation reproduction study is given but no evaluation of the validity of the study.

- only occasionally, there is information on the number of animals included in the teratogenicity studies.

- there is no information on the study parameters.

- NOAEL values for teratogenicity are given.

- there is no information on the quality of the data, whether the studies were performed according to GLP, whether they follow any testing criteria, and no judgement on the acceptability of the studies.

- the review contains a summary and a toxicological evaluation including NOAEL's, ADI-value, and recommendations for future studies.

2.7 General impressions about similarities and differences in data review types

- there is no uniformity concerning the extent, the disposition (sometimes there is a chapter on "Irritation", sometimes "Irritation" is included in the chapter on acute toxicity), the chapter headings (see above: I. Introduction), and the general terminology.

- the British review is the only document that contains information on the ecotoxicological effects. (In Sweden, usually two separate documents on a pesticide are produced, one on the toxicological effects and one on the ecotoxicological effects).

- the Swedish review is the only one having concluding remarks after each study noting if the study was performed according to the OECD Guidelines. It also is the only document which consistently validates the studies. Unfortunately, it is not translated to English.

- a table of contents is missing in some documents.

- sometimes there is a summary and an evaluation in the beginning of the review document, sometimes at the end, sometimes there is a summarizing part including comments at the end of each study section.

- some review documents only summarize the study results with insufficient conclusions and no judgment of the validity of the studies.

- there is no consistency in terminology: "short-term" - "sub-acute"; "chronic" - "long-term"; "teratology" - "developmental toxicity", etc.

- sometimes "reproductive toxicity" has an overall definition, sometimes it only involves effects on adults, or effects seen in one-, two-, or multigeneration studies.

- usually NOEL values are stated, only occasionally NOAEL's.

- generally, there is no information on biological or statistical significance.

- the A/D ratio (adult/developmental ratio) is only occasionally mentioned in the developmental studies.

- only one document considers toxicokinetic data in the evaluation of reproductive effects.

3 Comparison of values/results reported in the data reviews

Test areas for which comparisons are made are compiled in Tables I-VIII (Appendix 1). In some instances, several countries cited the same study. In such cases, the study is given one reference number along with endpoints and comments given by each country. When possible, studies cited by UK are also given reference numbers but these had to be deduced, as reference data were omitted in the British review document. A bibliography is enclosed (Appendix 2).

1. The participating countries have to a great extent reviewed the same studies. Australia has reviewed many more studies than the other countries, mainly due to the recent publication of the review document. Only occasionally, another country has presented a unique study. Of 29 documents concerning acute toxicity 22 were cited by Australia, 6 by Sweden, 10 by UK, 2 by the US, and 19 by FAO/WHO. Of 16 documents on developmental toxicity, 13 were cited by Australia, 6 by Sweden, 10 by UK, and 7 by FAO/WHO. Of 3 documents on multigeneration studies, all were cited by Australia, 2 by Sweden, 2 by UK, 1 by the US, and 1 by FAO/WHO.

2. The countries have focused on the same endpoint in the acute toxicity studies (lethal dose studies).

The Australian review document was used as a reference when comparisons concerning the endpoints of developmental and reproductive toxicity were made. This document covers most of the studies. The participating countries reported about 55% of the developmental endpoints noted in the Australian document and about 70% of all the endpoints recorded in the multigeneration studies. However, the other countries may have included endpoints not noted in the Australian review.

3. The countries have mainly focused on the same endpoints in assessing the pesticide's maternal and foetal toxicity and teratogenicity.

4. In those cases NOEL/NOAEL values are noted, no different values are reported.

5. There are gaps in the review data between the countries; however, these are judged to depend mainly on different publication years of the documents.

The **conclusion** about Dinocap's **acute toxicity** is rather uniform:

- **Australia:**

low acute oral toxicity in rats and rabbits, moderate toxicity in mice and dogs; low acute dermal and inhalation toxicity in rabbits and rats, respectively.

- **Sweden:**

moderate acute oral toxicity, low acute dermal and inhalation toxicity.

- **UK:**

moderate acute oral toxicity to rats and mice low acute dermal toxicity to rabbits, and low acute inhalation toxicity to rats.

- **FAO/WHO:**

low acute oral toxicity to the species examined (according to table: rat, mouse, rabbit, and dog).

The **conclusions** about Dinocap's **reproductive, including developmental, hazard** are as follows:

- **Australia:**

Reproductive toxicity: unaffected reproduction and male fertility.
Developmental toxicity (oral route): species specific (mouse a sensitive species; equivocal evidence of teratogenicity in rabbits; no teratogenic potency in the rat and hamster). No developmental toxicity in rabbits following dermal administration.

- **Sweden:**

Reproductive toxicity: no unambiguous substance-related effects on reproduction.
Developmental toxicity: indications on teratogenic effects in rabbit and mouse.

- **UK:**

Reproductive toxicity: no adverse effects in a three-generation study.
Developmental toxicity, rabbit, oral route: NOEL for maternal toxicity 3 mg/kg for foetal toxicity and teratogenicity 12 mg/kg.
Dermal route: no evidence of teratogenicity at 200 mg/kg in the rabbit.
Mouse, oral route: NOEL for maternal toxicity 40 mg/kg/day, NOEL for teratogenicity 10 mg/kg/day.
Rat and hamster, oral route: no evidence of teratogenicity.

- **US:**

Dinocap is a developmental toxicant in laboratory animals, specifically in rabbits, by the oral route.

- **FAO/WHO:**

Reproduction/teratology study: no compound-related effect in the rat.
Developmental toxicity: apparent order of species sensitivity: rabbit > mouse > hamster > rat.
Rabbit, oral route: NOAEL 0.5 mg/kg/day
Rat, oral route: NOAEL 100 mg/kg/day

There is a unanimous conclusion that Dinocap has a teratogenic potential. However, one review identifies the mouse as the sensitive species, while two others identify the rabbit as the most sensitive species.

4 Potential for use of reviews by other countries in lieu of conducting a separate review

The review documents from Australia, the UK, and FAO/WHO, and the separate US study reports can be used as complements to our own review. The assessment of a separate study made by another country may be accepted. However, the available basic data differs to a great extent between countries. Furthermore, comments and conclusions often have certain limitations as there often is inadequate or no information on the acceptability and validity of the study, studied parameters, statistical or biological significance, dose-response relationship, whether the study has followed any guidelines, if the substance is a specific developmental toxicant or not, species sensitivity, consideration of toxicokinetics, mechanisms, and comparison to historical control data. If accessible, this information is of great importance for the final evaluation.

The reviews from Australia and Sweden are well-arranged with each study and each chapter clearly defined. Relevant information on methodology, study parameters, study results, and references is included as well as summarizing tables.

The Swedish review includes comments to each study and each chapter which is a great advantage in the evaluation procedure. This document also includes information on whether the studies are/are not performed according to the OECD Guidelines.

5 Recommendations

A review document following uniform principles as presented in "Guidelines for Preparing Chemicals Reviews" (Report by an OECD Expert Group, 1984) would increase the possibility for the OECD Member Countries to use each other's reviews.

The OECD Guidelines may, however, need to be revised for this Pesticide Project.

A Nordic guideline for the content of a pesticide review is enclosed (Appendix 3).

It is important that there is a concordance in terminology.

It is of great value if each study is discussed separately.

It is desirable to have summary tables and conclusive comments in each chapter.

Appendices

Appendix 1. Tables

Table I. Number of Specified Acute Toxicity Studies

Study type		Australia	Sweden	UK	FAO/WHO
Acute oral -rat	AI FM	13 2	2 -	10 2	14 -
Acute oral -mouse	AI FM	5 -		- 2	5 -
Acute oral -rabbit	AI FM	3 -			2 -
Acute oral -dog	AI FM	2 -			1 -
Acute dermal -rat	AI FM			- 1	
Acute dermal -rabbit	AI FM	3 2	2 -	1 1	2 -
Acute inhalation -rat	AI FM	2 1	1 -	(2)[a] 1	2 -
Acute i.p. -rat	AI FM	3 -	2 -	1 -	4 -
Acute i.p. -mouse	AI FM	1 -			
Acute i.v. -rat	AI FM	2 -	1 -		1 -
Acute s.c. -rat	AI FM	1 -	1 -		1 -
Acute s.c. -mouse	AI FM	1 -	1 -	1 -	
Dermal irritation -rabbit	AI FM	1 3		1 -	1 -
Dermal irritation -guinea pig	AI FM	1 -			
Eye irritation -rabbit	AI FM	2 1		2 1	
Toxicity to aquatic organisms	AI FM			11 -	
Toxicity to beneficial insects	AI FM			1 -	

[a]) species not specified in one study

Table II. Acute Toxicity Studies of Dinocap (Technical Grade) in Mammals

LD_{50} (mg/kg) / LC_{50} (mg/m^3)						
Ref.	**Study type**	**Endpoint**	**Australia**	**Sweden**	**UK**	**FAO/WHO**
	Oral route					
1	***Mouse***, ♂	LD_{50}	# 200		#	#
2	", "	"	# 86		#	#
2	", ♀	"	# 95		#	#
3	", ♂	"	# 180		#	#
3	", ♀	"	# 150	#		#
4	", ♂	"	# 50			#
4	", ♀	"	57			
5	", ♂/♀	"	# 265			#
3	Rat, ♂	"	# 2 171		#	#
3	", ♀	"	# 1 212		#	#
6	", ♂	"	# 1 581		#	#
7	", ♂	"	# 1 872		#	#
8	", ♂	"	# 2 139		#	#
9	", ♂	"	# 1 985		#	#
10	", ♂	"	# 1 581-2 321		#	#
?	", (sex not specif.)	"			1 670	
11	", ♂	"	# 635		#	#
11	", ♀	"	# 510		#	#
12	", (sex not specif.)	"	#> 5 000 (purity unknown)		#	#
13	", ♂	"	# 980	#		#
14	", ♀	"	# 1 190	#		#
4	", ♂	"	# 1 180			#
4	", ♀	"	# 1 108			#
15	", ♂	"	# 1 175			#
15	", ♀	"	# 1 493			#
5	", ♂/♀	"	780			

LD_{50} (mg/kg) / LC_{50} (mg/m^3)						
Ref.	**Study type**	**Endpoint**	**Australia**	**Sweden**	**UK**	**FAO/WHO**
16	", ♂	"		714		
14, 17	***Rabbit***, ♂	"	# approx. 2 000			#
4	", ♂	"	# approx. 3 000			#
14, 24	Dog, ♂/♀	"	# approx. 100			#
	Dermal route					
13, 14	***Rabbit***, ♂	LD_{50}	# > 4 700 (conc. 50%)	#		#
12	", (sex not specif.)	"	# > 2 000 mg/kg		#	#
	Inhalation					
19	***Rat***, ♂/♀	LC_{50}	# > 20 840, 4h (coarse)	#	#	#
19	", "	"	# > 660, 4h (fine)	#	#	
12	", (sex not specif.)	"	# > 20 200, 1h		#	#
	Intraperitoneal route					
20	***Mouse***, ♂	LD_{50}	# 200	#		#
20	", ♀	"	# 178	#		#
20	***Rat***, ♂	"	# 388	#		#
20	", ♀	"	# 370	#		
21	", ♂/♀	"	# 433	#	#	#
15	***Rat***, ♂	"	# 48 (5% aq. Tween 80)			#
15	", ♀	"	# 57 (5% aq. Tween 80)			#
	Intravenous route					
14, 22	***Rat***, ♂	LD_{50}	# 23		#	#
	Subcutaneous route					
20	***Mouse***, ♂	"	# 520	#		#
20	", ♀	"	# 480	#		#
20	***Rat***, ♂/♀	"	# > 2 000	#		#
LD_{50} values are available for available for isomers, metabolites, and end-use products			#		#	

Table III. Acute Toxicity of Aquatic Organisms

Ref.	Species	Endpoint LC_{50} (mg/l)		Result	Country/ Organization
18	Gammarus fasciatus	24h 96h	0.120 0.075	Dinocap would be hazardous to fish and fish food species	UK
18	Rainbow trout	24h 96h	0.015 0.015		
23	Rainbow trout	24h 48h	0.014 0.014		
18	Goldfish	24h 96h	0.045 0.033		
23	Goldfish	24h 48h	0.09 0.08		
18	Bluegill Sunfish	24h 96h	0.029 0.026		
23	Catfish	24h 48h	0.17 0.17		
23	Harlequin	24h 48h	0.56 0.44		
23	Daphnia Magna	EC_{100} (µg/ml)	0.05		
23	Scenedesmus subspicatus	EC_{10} (mg/l)	4.3		
23	Scenedesmus subspicatus	EC_{50} (mg/l)	31.5		

Table IV. Toxicity to Beneficial Insects

Ref.	Species	Endpoint		Value/Result	Country/ Organization
47	Honey bee	L_{50} (µg/bee)	33.39	Does not indicate a hazard to this organism	UK

Table V. Irritation

Ref.	Species	Endpoint	Value/Result	Country/ Organization
	Skin irritation			
13	Rabbit	25% WP FM: moderate erythema 25% EC FM: moderate erythema and oedema		Australia
25	Rabbit	FM: slight to moderate oedema	Moderate skin irritant	Australia
4	Rabbit	AI: ≥5% sol.: moderate erythema and oedema 2.5%: reversible slight irritation	≥5%: moderate skin irritant; 2.5%: slight skin irritant	Australia
26	Rabbit	FM: reversible slight erythema		Australia
?	Rabbit	AI: Slight to moderate erythema Slight to severe oedema		UK
27	Rabbit	AI: ≥0.5 cc/kg: moderate to marked skin irritation		FAO/WHO
4	Guinea pig	100%: erythema 10%: slight erythema 1-2.5%: extensive erythema at repeated dosing		Australia
	Eye irritation			
12	Rabbit	AI: -conjunctival redness -chemosis -discharge -corneal opacity	Severe eye irritant	Australia
?	Rabbit	AI: -moderate corneal opacity -iris lesions -moderate to severe conjunctivitis and chemosis		UK

Ref.	Species	Endpoint	Value/Result	Country/ Organiza-tion
?	Rabbit	AI: -corneal, iridial and conjunctival effects		UK
25	Rabbit	FM: -moderate to severe conjunctival and iridial effects -corneal opacity -deaths	Severe eye irritant	Australia
25	Rabbit	FM: -severe conjunctival irritation	Irritant to eyes	UK
28	Rabbit	FM: -moderate to severe conjunctivitis -slight corneal damage -iritis -corneal opacity	Severe eye irritant	Australia

Table VI. Development Toxicity, Oral Studies (AI)

Ref.	Species	Endpoint	Value/Result	Country/ Organization
32	Mouse	AI: (high purity): -increased number of resorptions -decreased litter sizes -decreased foetal b.w. -pup mortality -reduced pup survival -reduced pup b.w. -cleft palate -open eye lids -torticollis -decreased b.w. and b.w. gains -effects on swimming	The NOEL for materno-toxicity = 10 mg/kg/day; the NOEL for foetotoxicity = 4 mg/kg/day; the NOEL for teratogenicity = 4 mg/kg/day	Australia
33	Mouse	AI: (74%) -increased maternal mortality -decreased maternal b.w. gain -increased relative maternal liver weights	The NOEL for materno-toxicity = 40 mg/kg/day; the NOEL for toetotoxicity < 10 mg/kg/day; the NOEL for teratogenicity = 10 mg/kg/day	Australia
33	Mouse	-decreased maternal b.w. gain -decreased gravid uterine weights -decreased foetal b.w. -cleft palate -foetal death	The NOAEL for embryo/foetotoxicity = 10 mg/kg b.w./day	FAO/WHO
34	Mouse	AI: (84%) -decreased foetal b.w. -cleft palate -decreased number of live pups per litter -torticollis -swimming behaviour deficits -otolith agenesis	The NOEL for materno-toxicity = 25 mg/kg/day; the NOEL for foetotoxicity or teratogenicity = 25 mg/kg/dose	Australia
34	Mouse	-reduced foetal weight -postnatal death -retarded growth -torticollis -swimming defects -cleft palate		UK

Ref.	Species	Endpoint	Value/Result	Country/ Organization
35	Mouse	AI: (84%) -mortality -reduced foetal b.w. -increased mortality -lower otolith development scores	The NOEL for materno-toxicity = 30 mg/kg/day; the NOEL for foetotoxicity = 10 mg/kg/day	Australia
36	Mouse	-increased mortality -decreased b.w. -cleft palate -headtilt -behavioural effects -retarded development of the otoliths -increased locomotor activity	The NOEL for materno-toxicity = 25 mg/kg/day; the NOEL for developmental toxicity = 12 mg/kg/day	Australia
36	Mouse	-increased postnatal mortality -cleft palate -torticollis	Indications on teratogenic effects ≥ 12 mg/kg/day	Sweden
36	Mouse	-torticollis -swimming abnormalities -inner ear malformations -otolith defects		UK
?	Mouse	-maternal deaths -reduced maternal b.w. gain -decreased foetal weight -reduced foetal viability -foetal death -resorptions -cleft palate -hydronephrosis -delayed skeletal ossification	The NOEL for maternal toxicity = 40 mg/kg; the NOEL for terato-genicity = 10 mg/kg. A NOEL for foeto-toxicity was not established based on foetal weight	UK
36, 38	Mouse	-increased pup mortality -decreased foetal weight -torticollis -missing otoliths -effect on swimming ability -agenesis of otoconia	No maternal toxicity The NOAEL for embryo/ foetotoxicity = 6 mg/kg b.w./day	FAO/WHO
37	Mouse	-reduced postnatal survival -balooned g.i. tracts -cleft palate -reduced pup b.w. -torticollis		UK
37	Mouse	The same endpoints as described by Australia in ref. 36	The NOEL for otolith development = 6 mg/kg/day	Australia

Ref.	Species	Endpoint	Value/Result	Country/ Organization

45	Mouse	-reduced maternal b.w. gain
		-reduced number of corpora lutea
		-reduced number of implantations
		-reduced litter size
		-reduced foetal b.w.
		-resorptions
		-increase in dead conceptuses/litter
		-cleft palate
		-open eye lids
		-head tilt
		-effects on swimming performance
			The NOEL for maternal toxicity = 10 mg/kg;
			the LOEL for maternal toxicity = 25 mg/kg;
			the NOEL for developmental toxicity = 4 mg/kg;
			the LOEL for developmental toxicity = 10 mg/kg
				US

36	Rat	-reduced maternal b.w. gain		UK
36	Rat	-reduced maternal weight gain	The NOAEL (not specified) = 100 mg/kg b.w./day	FAO/WHO
36	Rat	-reduced maternal b.w. gain	The NOEL for maternotoxicity = 50 mg/kg/day; the NOEL for developmental toxicity = 100 mg/kg/day	Australia
36	Rat	-reduced maternal b.w. weight gain	No indications on teratogenic effects	Sweden
38	Rat	-reduced maternal b.w. weight gain and food consumption	The NOEL for maternotoxicity = 50 mg/kg/day. No teratogenicity or foetotoxicity at 150 mg/kg/day	Australia
39	Rat	-reduced maternal b.w. gain -increased mortality -increased relative liver weights -reduced foetal b.w. -increased foetal mortality -resorptions	The NOEL for maternotoxicity = 100 mg/kg/day. No teratogenicity at 200 mg/kg/day	Australia
39	Rat	-increased mortality -reduced b.w. gain -increased number of dead or resorbed implants -reduced foetal weight -cerebral ventricle dilation -delayed skeletal ossification -supernumerary ribs -misaligned sternebrae	The NOEL maternal and foetotoxicity = 100 mg/kg/day; A/D ratio = 1	UK
39	Rat	-reduced maternal weight gain -reduced foetal weight gain	The NOAEL (not specified) = 100 mg/kg b.w./day	FAO/WHO

Ref.	Species	Endpoint	Value/Result	Country/ Organization
35	Hamster	AI (84%): -maternal mortality -reduced maternal extrauterine weight gain -reduced foetal weight -increased foetal mortality -lower otolith scores	No NOELs for materna-toxicity or foetoxicity were established (effects at all dose levels)	Australia
36	Hamster	AI (84%) -reduced maternal weight gain -resorptions -reduced pup viability -reduced organ weights -reduced growth -reduced litter weights	The NOEL for maternal toxicity = 50 mg/kg/day; the NOEL for foetotoxicity = < 25 mg/kg/day	Australia
36	Hamster	-resorptions -maternal mortality -reduced weight gain postnatally	No indications on teratogenic effects	Sweden
36	Hamster	-reduced litter weight		FAO/WHO
38	Hamster	-decreased maternal weight gain -decreased foetal weights -hydronephrosis	The NOAEL (not speci-fied) = 12.5 mg/kg b.w./day	FAO/WHO
39	Hamster	-increased mortality -reduced maternal b.w. gain -reduced foetal viability -increased number of dead or resorbed implants -reduced foetal weight -renal pelvis dilation -hydronephrosis -reduced skeletal ossification -decreased (sic) incidence of super-numerary ribs	The NOEL for maternal toxicity < 12.5 mg/kg; the NOEL for foeto-toxicity = 12.5 mg/kg; A/D ratio < 1	UK
39	Hamster	AI (84%) -reduced maternal weight gain -maternal mortality -decreased foetal weight -reduced number of sternal and caudal ossification centers	No maternal NOEL was established (effects at all dose levels); the NOEL for foetotoxicity = 12.5 mg/kg/day No teratogenicity	Australia

Ref.	Species	Endpoint	Value/Result	Country/ Organization
40	Rabbit	-maternal mortality -abortions -resorptions -discoloured urine -mucoid intestinal contents -reduced stool volume	A NOEL for materno-toxicity was not established (effects at all dose levels); no foetal toxicity at 10 mg/kg/day	Australia
40	Rabbit	-maternal deaths -coloured urine -reduced faetal output -abortions -reduced mean foetal weight		UK
41	Rabbit	AI (technical grade): -abortions -reduced maternal b.w. -reduced stool volume -discoloured urine -reduced foetal b.w. -increased post implantation embryo loss -increased incidence of reduced ossification and bent hyoid arches -hydrocephalus -small pinna -scoliosis	the NOEL for materno-toxicity = 3 mg/kg/day; no NOEL for developmental effects (no dose -related malformations at 3 mg/kg/day)	Australia
41	Rabbit	-maternal mortality -abortions/resorptions -reduced stool volume -reduced maternal b.w. gain -reduced foetal viability -reduced foetal b.w. -increased incidence of bent hyoid arches -delayed ossification -skeletal malformations such as scoliosis -cleft palate -hydrocephalus	Teratogenic effects at lower dose levels than for maternal toxicity; embryotoxic effects ≥12 mg/kg/day; foeto-toxic effects ≥ 48 mg/kg/day	Sweden

Ref.	Species	Endpoint	Value/Result	Country/ Organization
41 ?	Rabbit	-abortions -stained fur -coloured urine -reduced maternal b.w. gain -decreased viability indec -decreased gestation index -resorptions -reduced foetal weights -malformations -bent hyoid arches -delayed ossification	The LOEL for maternal toxicity = 12 mg/kg; the NOEL for foetotoxicity was not established based on the increased incidence of resorptions. Unclear teratogenic potential	UK
41 ?	Rabbit	-maternal deaths -reduced maternal b.w. gain and food consumption -anorexia -abortion and/or resorption -early delivery -coloured urine -stained paw -absence of faeces or dried faeces -alopecia -reduced litter size -reduced foetal b.w. -skeletal malformations -hydrocephaly	The NOEL for maternal toxicity and foetotoxicity = 12 mg/kg. No overt evidence of teratogenicity	UK
41, 42	Rabbit	-postimplantation losses -hydrocephaly -normal tube defects	Maternal toxicity at ≥100 mg/kg	FAO/WHO
42	Rabbit	-coloured urine -reduced faetal output -reduced b.w. gain -abortions -resorptions -reduced foetal viability	The NOEL for maternal and foetotoxicity = 0.5 mg/kg. No evidence of teratogenicity	UK
42	Rabbit	-coloured urine in does -reduced stool volume in does -abortions -reduced maternal b.w. -increased post implantation losses -reduced foetal viability -decreased litter sizes	The NOEL for maternal toxicity and foetotoxicity = 0.5 mg/kg/day. No teratogenic activity up to 48 mg/kg/day	Australia

Ref.	Species	Endpoint	Value/Result	Country/ Organization
42	Rabbit	-reduced stool volume -coloured urine -reduced maternal b.w. -abortions -resorptions -reduced foetal viability -reduce foetal b.w.	Maternal toxicity and also embryotoxic and foetotoxic effects at 48 mg/kg/day	Sweden
46	Rabbit	-gastric ulcerations in does -decreased maternal b.w. gain and food consumption -increased maternal wastage -mortality -decreased foetal b.w. -growth inhibition -skeletal alterations -malformations	The NOEL for maternal toxicity = 3 mg/kg; the NOEL for developmental toxicity = 12 mg/kg	US

Table VII. Development Toxicity, Dermal Studies

Ref.	Species	Endpoint	Value/Result	Country/ Organiza-tion
43	Rabbit	-irregular faeces -skin irritation -reduced maternal b.w. gain and food intake	No NOEL for maternal toxicity was established (poor dermal absorption)	Australia
43	Rabbit	-reduced maternal b.w. gain and food consumption -skin irritation	No embryotoxic or toetotoxic effects	Sweden
43	Rabbit	-skin irritation -reduced food consumption -decreased b.w. gain -decreased mean foetal weight	The NOEL for maternal toxicity was not established based on skin irritation, but was 50 mg/kg/day based on weight changes and food intake. The slightly reduced foetal weight at 100 mg/kg/day was probably associated with decreased maternal b.w. gain	UK
43	Rabbit	-skin irritation -delayed ossification -skull abnormalities	Maternal toxicity at 100 mg/kg b.w./day. The NOAEL for embryo/foeto-toxicity approx. 100 mg/kg b.w./day	FAO/WHO
44	Rabbit	-reduced foetal output -anorexia -abnormal gain -reduced maternal b.w. gain -skin irritation -increased resorptions -reduce foetal weight	No NOEL for maternal toxicity was established The NOEL for foetotoxicity = 100 mg/kg/day. No evidence of teratogenic potential	Australia
44	Rabbit	-skin irritation -reduced b.w. gain -resorptions	No malformations and no treatment related variations	UK
44	Rabbit	-skin irritation -resorptions and/or abortions -reduced foetal weight		FAO/WHO

Table VIII. Multigeneration Oral Studies (AI)

Ref.	Study type	Endpoint	Value/Result	Country/ Organiza-tion
	Two generation study			
29	Rat	-decreased b.w. and food consumption -increased mortality	NOEL = 200 ppm (10 mg/kg/day)	Australia
29	Rat	-pup mortality -decreased b.w. gain and food consumption -decreased pup weight /litter (F_1) -decreased liver weights	Systemic parental NOEL = 200 ppm (12.9-18.0 mg/kg/day); systemic parental LOEL = 1 000/400 ppm (65.1-77.3/32.4-38.7 mg/kg/day); reproductive NOEL = 200 ppm (12.9-18.0 mg/kg/day); reproductive LOEL = 1 000/400 ppm (65.1-77.3/32.4-38.7 mg/kg/day)	US
	Three generation study			
30	Rat	None	No findings at 200 ppm (10 mg/kg/day)	Australia
30 ?	Rat	None	NOEL 200 ppm (10 mg/kg/day)	UK
30	Rat	None	No treatment -related reproductive or developmental effects at 200 ppm	Sweden
30	Rat	None	NOAEL = 200 ppm (6.4 mg/kg b.w./day)	Sweden

Ref.	Study type	Endpoint	Value/Result	Country/ Organiza-tion
	Four generation study			
31	Rat	-weakness -decreased b.w. gain and food intake	No effect on reproduction or litter parameters (F_o 56 mg/kg, F_1 110 mg/kg, F_2 121 mg/kg, F_3 107 mg/kg	Australia
31 ?	Rat	-reduced pup survival in F_2	No effect on the length of gestation, fertility indices, or on the number of live pups born. Reduced pup survival in the 2nd generation (F_1-F_3)	UK
31	Rat	-decreased survival -reduced lactation -decreased parental b.w.	0.5% of the LD_{50} caused decreased survival and lactation, and decreased parental b.w.	FAO/WHO

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   6.2 Distribution

   6.3 Metabolism

   6.4 Excretion

   6.5 Conclusions on toxicokinetics

   TOXIC EFFECTS

   Each evaluation of the various types of toxicity should have a concluding part with an evaluation of the major findings and an assessment of associated hazards.

   The quality of each study should be validated. An introductory section on mechanisms of toxicity should be included in those cases where this is known.

7. ACUTE TOXICITY OF ACTIVE INGREDIENT AND FORMULATIONS
Data on formulations are presented when practicable

7.1 Acute oral toxicity

7.2 Acute dermal toxicity

7.3 Acute inhalation toxicity

7.4 Acute toxicity by other routes of administration

8. IRRITATION OF ACTIVE INGREDIENT AND FORMULATIONS

8.1 Eye irritation

8.2 Skin irritation

9. SENSITIZATION

10. SUBACUTE AND SUBCHRONIC TOXICITY

11. CHRONIC TOXICITY/CARCINOGENICITY

12. GENOTOXICITY

12.1 Gene mutations

12.2 Chromosomal aberrations

12.3 DNA effects

13. REPRODUCTIVE TOXICITY

13.1 Multigeneration studies

13.2 Teratogenicity

13.3 Other effects

14. NEUROTOXICITY

15. BIOCHEMICAL EFFECTS

16. TOXIC EFFECTS IN HUMANS

17. TOXIC EFFECTS OF IMPURITIES/METABOLITES
(when data are available)

18. INTERNATIONAL EVALUATIONS

19. CONCLUSIONS

Overall evaluation of the data, with special reference to mechanisms of toxicity, dose-response relationships and no-effect levels.

20. REFERENCES

ANNEX 5

PHASE 3 REPORT

ON

ENDOSULFAN

Lead Country: United States

Contents

1 Introduction

The following countries submitted data review reports on endosulfan for the various disciplines:

- **Toxicology and metabolism**

Australia, Canada, Denmark, FAO, Germany, Sweden, United States

- **Fate and behavior in the environment**

Denmark, Germany, Sweden, United States

- **Ecotoxicology**

Denmark, Germany, Sweden, United States

A bibliography for all of the disciplines was received from Finland. However, no reviews of data were provided for environmental fate and ecotoxicology. The toxicology review included information on the individual studies but it was difficult to match the reviews to the references. Therefore, the Finland reviews were not used in this Phase 3 report.

This report will focus on the following study areas within each discipline:

- **Toxicology**

Acute toxicity
Subchronic toxicity (repeated dose dermal-28 days)
Developmental and reproductive toxicity
Chronic toxicity and carcinogenicity
Neurotoxicity

- **Environmental fate**

Hydrolysis
Photodegradation in water
Soil metabolism, aerobic and anaerobic
Mobility/leaching
Adsorption/desorption
Extent and nature of bound residues in soil

- **Ecological effects**

Avian testing
    Avian acute oral toxicity
    Avian dietary toxicity; terrestrial and aquatic
    Avian reproduction; terrestrial and aquatic

Aquatic testing
    Freshwater fish acute toxicity; warmwater and coldwater species
    Daphnia acute immobilization test
    Marine, estuarine fish acute toxicity
    Daphnia life cycle
    Chronic toxicity to fish and fish early life stage

- **Beneficial insects, non-target species**

Acute toxicity to honeybees
Acute toxicity to earthworms

- **Phytotoxicity to non-target plants**

Algae, growth inhibition

2 Types of data reviews

The following documents were used in Phase 3:

Australia:
Endosulfan - Review of Mammalian Toxicology and Toxicokinetic/Metabolism Data. June 1993.

Canada:
Endosulfan Toxicity Summary and Individual Study Reviews.

Denmark:
Toxicological Evaluation of Endosulfan. May 1993
Ecotoxicological Evaluation of Endosulfan. June 1993.

FAO:
Pesticides Residues in Food - Endosulfan, 1989.

Germany:
Data Evaluation of Toxicological and Metabolism Studies, Feb. 1993.
Evaluation of Endosulfan. March 5, 1993

Sweden:
Toxicological Evaluation of the Insecticide Endosulfan. March 1990.
Ecotoxicological Evaluation of the Insecticide Endosulfan. November 1992.

US:
Individual Study Reviews
Endosulfan Pesticide Registration Standard, April 1982.

2.1 Toxicology

In general the different countries' reviews of health effects data were sufficiently detailed and comprehensive to allow a conclusion about the studies referred to. However, some differences in approach were also apparent which are discussed country-by-country below.

2.1.1 Australia

Australia presented the results of acute toxicity tests in tabular form. The evaluation of individual studies was short and concise, listing briefly the design of the study as well as the major findings, including the NOEL and significant toxic effects. The reviews were basically summaries of the studies and, therefore, were not comprehensive and detailed, addressing for example all the parameters studied, and/or providing summary tables of findings. The original language of these reviews is English.

Little information regarding the quality of the studies and their compliance with GLP or OECD guidelines is provided. Major deficiencies in studies are mentioned.

Reviews of individual studies provided a conclusion (e.g. NOEL for that study or "no carcinogenic effects were noted"). However, because of the brevity of the reviews, it was not entirely clear to what degree these findings were based on an independent analysis by the reviewer. An overall conclusion, such as an ADI, was not provided.

2.1.2 Canada

The Canadian reviews of each individual study, including acute toxicity tests, were very complete and comprehensive. Each study was evaluated in detail and the independent work of the reviewer was quite apparent. In fact the review clearly compared the study director's evaluation with that of the government toxicologist. The reviews contain discussions of all parameters studied, and conclusions are supported by presentation of data in tables or other comprehensive form.

In addition to the detailed review of each study, a summary description of the major findings is provided. This summary is similar to the one described for Australia, possibly somewhat shorter, since details can be found in the comprehensive part of the review package.

Particular reference to OECD guidelines or GLP is not provided. However, the detailed review and discussion by the reviewer clearly provide an understanding of the quality and acceptability of the study.

Clear conclusions about each study are provided. No ADI for the chemical is given.

2.1.3 Denmark

The reviews by Denmark, including those for acute toxicity testing, were fairly extensive and complete and presented a "methods" section, results and conclusions. A clear identification of the study reviewed was given and the reviewer presented some of his/her judgements concerning the quality and reliability of studies.

NOELs and major toxicological effects are given for each study reviewed but an ADI for the chemical is not determined in the submission for the Pilot Project.

The reviews were translated from Danish into English for the purpose of the Pilot Project.

2.1.4 Germany

The German review report is basically in a summary form. A table of the results of the acute toxicity studies is presented. In general the individual study reviews are somewhat longer than those done by Australia for example. For the most important studies the reviewer provided some degree of discussion of the results; older studies in the same species were mentioned only very briefly, more or less as background information.

For each study reviewed a NOEL is provided but an ADI is not established.

The reviews were translated from German into English for the purpose of the Pilot Project.

2.1.5 Sweden

The Swedish report presents a table of results for oral, dermal and inhalation studies. The reviews of individual studies are more detailed and technical than those done by Germany and Australia, for example, and are comparable to those done by Denmark. Individual parameters are analyzed and discussed and toxic effects are described. The Swedish reviews are quite comprehensive but not to the degree found in the Canadian reviews.

The Swedish reviews consistently refer to compliance with the OECD guidelines, and this compliance seems to be an important factor in accepting a particular study as valid.

The Swedish reviews do not provide a summary conclusion nor give a NOEL for studies. In reading the review one could deduce the NOEL in most instances, but this process obviously could introduce reader judgement.

The Swedish review does not provide an ADI for the chemical, but does discuss ADI (RfD) considerations made by the US EPA. Incidentally, the EPA RfD discussed in the Swedish document was a preliminary one, and it is now changed.

The reviews were translated from Swedish into English for the purpose of the Pilot Project.

2.1.6 United States

The United States submitted individual study reviews called Data Evaluation Records (DER's). These studies, including those for acute toxicity studies, are very detailed and comprehensive and in may ways similar to the Canadian ones. However, in many cases data from the same study have been reviewed several times primarily because the first review requested additional information and clarification concerning the data. This practice often creates the impression that a "different" conclusion has been reached for a particular study when in fact an earlier conclusion has been revised based on additional data. For persons not familiar with the US review process this could be very confusing when trying to determine the "final" US conclusion concerning a study.

The US reviews generally do not address compliance with GLP[2] or OECD guidelines, but they do address compliance with EPA pesticide test guideline requirements.

A NOEL for the studies was provided by the reviews and major toxicologic effects were summarized.

The reviews of the "chronic toxicity" data base (carcinogenicity study in rats and mice, chronic study in dogs, multigeneration reproduction study, developmental toxicity studies in rats and rabbits, and supporting subchronic studies) were reviewed by the EPA's Pesticide Program Peer Review Committee as well as its Reference Dose (RfD) committee. For the review by the RfD committee, a summary of each study was prepared containing a synopsis of the study design, the major toxicological effects, and a determination of the NOEL. An ADI (or RfD) is also provided: 6E-3 mg/kg/day based on the NOEL in the chronic rat and chronic dog studies of about 0.6 mg/kg/day. (N.B. Information (study citation, summaries of major studies and the ADI) on chemicals such as endosulfan which have passed these peer reviews is electronically available to the public on EPA's Integrated Risk Information System (IRIS). For chemicals whose data base is not put on IRIS the science chapters of the re-registration document fulfill a similar function, i.e. providing the final summary conclusion of each study used in the identification of toxicological hazards.)

2.1.7 WHO/IPCS[3]

The data reviews by IPCS consist of fairly comprehensive summaries of the individual studies. There is sufficient discussion of the results to suggest that these summaries are based on a comprehensive review of the data. However, a detailed data review was not contained in the IPCS package.

The IPCS reviews do not refer to GLP or OECD guideline compliance, but the scientific validity of the data is addressed when necessary.

For each study the NOEL is provided. An ADI of 0.006 mg/kg/day is determined, based on NOELs in both the chronic rat and dog studies of about 0.6 mg/kg/day and a safety (uncertainty) factor of 100.

[2] Studies submitted to EPA however undergo an administrative check concerning GLP compliance before undergoing scientific review. The submitter of a study must certify GLP compliance. Therefore it can be presumed that any study reviewed was either certified to be in compliance with GLP or an explanation was provided why full GLP compliance was not possible (i.e. older studies). Any study submitted to the US EPA may also be subjected to a laboratory data audit.

[3] The WHO/IPCS review process is essentially a peer review where a reviewer presents his/her review to a panel of experts for evaluation and discussion. The summaries in the WHO/IPCS report then reflect the consensus conclusion of the expert panel for an individual study as well as for the overall assessment of the chemical.

2.1.8 Comparison of review packages

The review packages on the health effects of endosulfan can be grouped into categories depending on the level of detail provided in the review. In one category, the Canadian and US reviews are very comprehensive and detailed, providing detailed analyses on all major parameters studied. These type of reviews allow an understanding of the thought and review process which went into the evaluation of the studies. In a second category are the Swedish and Danish reviews, which are shorter but still comprehensive enough to provide an understanding of the review process and the independent analysis of the data. A third category includes the German and Australian reviews which are still more compact, but nonetheless provide a clear but brief description of the studies and the results. The review process for the third category is not quite as transparent as for the others.

The WHO/IPCS reviews probably should be placed in a category of their own, primarily because the review and evaluation process used by WHO/IPCS is clearly established. The scientific community fully understands the detailed and comprehensive data review which is initially performed, then reviewed by the panel of experts, and finally condensed in the consensus summary presented in the WHO/IPCS documents. In other words the summaries presented by WHO/IPCS are sufficient to provide the basic results of each study, but standing alone they would not provide much insight in the review and evaluation process. The lack of review documentation may be problematic for scientists who have not participated in IPCS workgroups, potentially including scientists in developing countries, and for regulatory managers, who may not be able to base national decisions on non-transparent evaluations by international experts.

The data review packages which were translated from the original language to English for the Pilot Project are mentioned in the description of the individual country descriptions of this section.

The evaluation of health effects studies and endpoints reported was similar. The possible minor exception was the evaluation and interpretation of developmental toxicity and reproduction studies. Several countries (mostly European) emphasized endpoints related to reproductive parameters. Other toxic effects were noted but were not considered to be pivotal. In the interpretation of developmental studies, countries consistently described teratogenic and embryo/fetotoxic effects, although the emphasis given to these effects varied.

2.2 Environmental fate and ecotoxicity

2.2.1 Denmark

Denmark's report on ecotoxicity and environmental fate devotes approximately 2-4 pages to a clear presentation and review of each study. Each study review includes a section on method, results, and reviewer's comments. For both environmental fate and ecotoxicity studies, the method section includes a fairly detailed discussion of how the study was conducted. The results of specific studies are usually presented in detailed tables. The comments section often contains a statement on whether the study was conducted according to an OECD or EPA guideline or some other standard procedure. If some deficiency was found with the study, that fact is also mentioned under the "comments" section along with any conclusions that can be drawn. A five page summary discussion and evaluation of all the data is included in the report.

The reviews were translated from Danish into English for the Pilot Project.

2.2.2 Germany

Germany's review of environmental fate data is organized by behavior of the chemical in soil, water, and air. The discussion under each section consists of summary statements about the chemical's behavior. References are sometimes given, but it is difficult to match up a statement with a specific study. There is no discussion of whether individual studies are conducted according to any formal guidelines except an occasional mention of an OECD or BBA guideline.

The review for ecotoxicity data is organized by organism (i.e., fish, earthworms, wildlife, bees, beneficial organisms). Information on acute toxicity is presented in summary tables and includes: for wildlife - species, sex, vehicle, LD_{50}, and study reference number; for fish - species, NOEC, LOEC, LC_{50}, duration of test. Summary one-line results are presented for other tests (early life cycle). Results from some field tests are summarized.

Overall it is difficult to match references of individual studies with the summary statements or the tables. Discussions of subchronic or chronic toxicity endpoints (avian chronic toxicity, reproduction) consist of summary paragraphs which briefly describe the study (dose levels, species tested, length of study) and the results. References are identified after each study discussion.

Estimated environmental concentrations are given for earthworms and water organisms. A risk assessment is presented for wild birds. Concluding statements regarding the toxicity of endosulfan to the organisms studied are included.

The review document was translated from German into English for the Pilot Project. Some bibliography citations are in German.

2.2.3 Sweden

The report submitted by Sweden includes: a one page summary of the results of the data; a tabular summary of the data; chapters on the chemical/physical properties of endosulfan, environmental fate, environmental effects; a hazard assessment; and a bibliography.

The environmental fate discussion is organized into three major sections: transport and distribution, transformation and bioaccumulation. Individual studies reviewed are discussed under topics within the three sections. The discussion of each study includes the study reference, a discussion of the study design method, the results (often presented in tabular form), and comments about the study. Included in the comments is whether the study was done according to a guideline, any deviations from that guideline or other study deficiencies, and any conclusions drawn about the chemical.

The environmental effects (ecotoxicology) chapter is organized in two sections: terrestrial organisms (microorganisms, earthworms, honey bees, non-target beneficial insects, birds) and aquatic organisms (alga, crustaceans, fish). The discussion of the studies in each section is structured in the same manner as the discussion of environmental fate studies.

Sweden's comments on the quality of the data note that a large number of studies had been included in the application for renewed registration of endosulfan, but that the quality of the studies varied and only those that were well-documented had been used for the ecotoxicological evaluation. Conclusions on the fate of endosulfan and ecotoxicity are presented. Some statements address the risk to some species but a formal, quantitative assessment is not included.

The review document was translated from Swedish into English.

2.2.4 United States

The United States submitted individual study reviews called Data Evaluation Records (DER's). Each review is comprehensive and includes: study reference, date of review, reviewer's name, a discussion of the study methodology, results, comments mostly pointing out study deficiencies, and conclusions (including if the study satisfies a guideline requirement). A comprehensive hazard and/or risk assessment is presented in the Registration Standard completed in April 1982.

2.2.5 Comparison of environmental fate and ecotoxicity review packages

The review packages on the environmental fate and ecotoxicity of endosulfan can be grouped into categories depending on the level of detail provided in the review and the format of the review. In one category, the reviews from Denmark and Sweden are similar in format and in the level of detail. Each of the reviews provides a clear reference to the study, a discussion of the methods and study results, evaluative remarks on the conformance to EPA or OECD guidelines, and a summary of the overall conclusions that can be drawn from the study. The individual study reviews are all presented in a comprehensive review document.

In another category are the reviews from Germany. These consist primarily of summaries of results from various studies. It was often difficult to match the study reference in the bibliography with the results presented in the review.

A last category consists of the US reviews. These reviews are on individual studies and are very comprehensive and detailed. An up-to-date comprehensive review document has not been done.

The evaluation of the fate and ecotoxicity studies and the respective numerical levels of the endpoints reported were uniform. Some countries evaluate the toxic effects on different fish species as well as earthworms. The summary remarks characterizing the hazard are also similar across all countries.

3 Comparison of values/results reported in the data reviews

A table based on the model presented in the Phase 3 Guidance, is presented in Appendix 1. The bibliographies to accompany each table (providing the citation for each study listed in the table) are presented in Appendix 2 (References).

The key findings based on an analysis of the table are presented below:

3.1 Toxicology

Acute toxicity (health effects)

More than 20 acute oral studies were reviewed by all countries combined. However, individual countries reported on only a portion of this total number. Canada and Germany reported results of 12 and 18 individual studies, respectively. Australia, Denmark and the US reported results of 6, 7, and 5 studies, respectively. Any one individual study may have been reviewed by as many as four (one study only) countries, but none of the studies was reviewed by all participating countries. In those cases where the results of a study were reported by more than one country, the results were identical. As expected, the LD_{50} values reported from the different studies were quite variable, ranging from a low of 9 mg/kg (in female rats) to a high of 125 mg/kg "in rats" (some higher values were reported on beta-endosulfan). The package from Denmark and WHO/IPCS did not contain acute oral study reports.

It is estimated that more than 1500 rats and other animals have been used over the years to "determine" the LD_{50} of endosulfan. The results of this effort are a determination that the female rat is more sensitive to acute intoxication, and that endosulfan is fairly toxic but not extremely toxic. Multiple review of the same acute oral toxicity study does not seem warranted, since identical values are reported by different reviewers and LD_{50} studies do not lend themselves to sophisticated toxicological interpretation. Likewise, multiple execution of the same study does not seem to improve significantly the knowledge concerning the acute toxicity of endosulfan.

For **acute dermal toxicity**, five studies were reported among all participating countries, three in the rabbit and two in the rat. One of the rabbit studies was reported by five of the six participating countries (WHO generally does not report on acute testing). The results reported from this as well as other studies with multiple reviews were identical for a particular study.

There was essentially one **acute inhalation study** reviewed by all participants, except the US and WHO/IPCS. All countries reported the same results.

A total of four **primary eye irritation studies** were reviewed by the participating countries (Sweden did not submit a review of an eye irritation study). One of these studies was reviewed by four countries (CA, DK, D, US). Their interpretations of the study results were very similar, but depended upon whether or not the reviewer focused on the cornea as the primary target of irritation. All reviews agreed however that endosulfan is not an eye irritant.

The situation was similar for the review of the **primary dermal irritancy study**. The same four countries (CA, DK, D, US) reviewed the same dermal irritancy study. The countries reported identical results, but their interpretations varied: the US called endosulfan "non irritating", Germany, "slightly irritating", Denmark concluded that "endosulfan can not be considered a primary irritant", and Canada found that "endosulfan is minimally irritating to the intact skin".

All countries and WHO/IPCS reviewed one **skin sensitization study**, and all concluded that endosulfan is not a dermal sensitizer.

Repeated dosing and special effects studies (human health effects)

In addition to evaluating the individual countries' reviews of long-term studies we have also consulted the summaries and conclusions on these studies submitted by the registrants. This process was not part of the directions for the Phase 3 evaluation, but we felt that it would be important to highlight agreements and disagreements between the conclusions reached by industry and the regulatory toxicologists. This comparison was done only for the major chronic mouse, rat, and dog study, the reproduction study, and the developmental studies in rats and rabbits.

A **neurotoxicity study in the domestic hen** was reviewed by all countries except Australia and WHO/IPCS. This study presumably was required at one time because of the neurotoxicological signs seen with endosulfan. All reviews agreed on the study results; the US moreover concluded that this study was inappropriate for this type of compound.

There were two **28 day repeated dermal dose** studies. One of the studies was reviewed by all countries and WHO/IPCS. The second study was reviewed by Canada, Denmark, the US and Sweden. Germany included the results of both studies in an overall conclusion about the dermal toxicity of repeated applications of endosulfan. There was some agreement on the results of the first study; however Canada and Denmark disagreed on the sensitivity of females in this study. The most striking difference in this area of dermal toxicity testing was the discrepancy between the results of the two studies, which were conducted during the same time period by the same author. This also explained the different interpretation of the study results by Germany since their evaluation included the results of both studies.

In the area of **chronic toxicity/carcinogenicity testing in the rat** there were three studies available to the reviewing countries: one a rather old study (1959), an NCI study, and an "up to date" chronic/carcinogenicity study. Some countries reviewed or mentioned the older and the NCI study but since both studies had major limitations (too few animals or high mortality), the results were considered of very limited value. The remaining study was reviewed and used by all countries except Sweden, and by WHO/IPCS; Australia did not present an independent review but relied on the evaluation by WHO/IPCS. The conclusions about the study were absolutely identical among the countries. The same conclusions were also reached by the study author.

There were two **carcinogenicity/chronic studies in the mouse** available for review, one of them done by NCI, the other by industry. The NCI study had significant problems with the survival of animals (males) and was therefore judged as "inconclusive" by those countries who mentioned it. Some of the countries did not include this study in the review. The industry-generated study was evaluated by all participating countries (Australia used the results of the

WHO/IPCS without independent review). The interpretations of the study results by the countries as well as by the study author were identical.

One (older) **chronic dog study** was reviewed by Australia, Germany and Sweden. The interpretation of the results as well as the conclusion concerning the study quality (deficient) was identical among the reviewing countries. The second (newer) dog study was reviewed by all countries except Australia and Sweden, and by WHO/IPCS. The conclusions concerning the results of the study were identical among the reviewing countries and matched the conclusion of the study author. An IBT dog study was mentioned by Germany and the US and was identified as deficient or invalid.

One **multigeneration reproduction study (rat)** was reviewed by all participating countries and WHO/IPCS (another "unusable"/"invalid" study was mentioned by Germany and the US). The description of the study results by the countries and the study director was identical. However, the interpretation of the results were different between the reviews. For example, most reviews assigned a NOEL of 15 ppm to the study based on a slight reduction in litter weights at 75 ppm. However, WHO and Sweden concluded that 75 ppm caused no effects on reproduction. Germany noted a threshold effect for slight toxicity at 75 ppm but noted no effect on reproduction at this level. The US reviewer on the other hand originally assigned a NOEL of 3 ppm to the study, based on toxicity (maternal liver weight increase). This conclusion was reversed in an internal EPA peer review and the NOEL was raised to 15 ppm.

One **developmental toxicity study in rabbits** was reviewed by all participating countries and WHO/IPCS. The reviews' conclusions concerning the results of the study were identical and were the same as that reported by the study author. There seemed to be a slight difference between countries in terminology and the significance placed on "teratogenic" effects, versus fetotoxic or embryo toxic effects.

One **developmental toxicity study in the rat** was reviewed by all countries except Denmark[4], and by WHO/IPCS. The description of the results of this study was identical between the countries and identical to the study author's description. However, the interpretation of the data was quite different. All reviews essentially agree with a NOEL for the maternal animals at 0.66 mg/kg/day. WHO, Canada, and Australia also seem to agree that 2.0 mg/kg/day is a NOEL for fetotoxic effects, i.e. some effects on the ossification and size of sternebrae are seen at 6.0 mg/kg/day. Germany and Canada also conclude that endosulfan is not teratogenic in the rat. Sweden concludes that endosulfan is embryotoxic in the rat at maternally toxic levels. The US on the other hand concludes that this study has no NOEL because there is a statistically significant increase of misaligned sternebrae in the lowest dose (0.66 mg/kg/day). This finding used by the US is also described in the conclusion by the study author, however the other reviewers seemed not to have attached any biological significance to this observation.

[4] Denmark presented a fairly detailed review of another rat study, but concluded that the study could not be used for a health effects assessment.The study reviewed by Denmark was done by IBT.

Summary

The table below shows the number of studies reviewed by each country for the various toxicology study areas.

	Aust	CA	DK	D	S	US	WHO
Acute oral	6	11	1	18	8	5	0
Acute dermal	2	2	1	2	2	2	0
Acute inhalation	1	1	1	1	1	1	1
Primary eye	2	3	1	1	0	3	0
Primary skin	2	2	1	1	0	2	0
Skin sensitization	1	1	1	1	2	1	1
Neurotoxicity	0	1	1	3	3	4	1
Repeated dose-dermal	1	2	2	1	2	2	1
Combined chronic /carcinogenicity rat	2	1	1	2	1	2	1
Chronic mouse	2	1	1	2	2	2	2
Carcinogenicity rat	1	0	0	1	1	0	1
Chronic dog	1	1	1	3	1	2	1
Developmental rabbits	1	1	1	1	1	1	1
Developmental rats	1	1	1	3	3	2	1
Reproduction	1	1	1	2	1	2	1

3.2 Environmental fate

Hydrolysis

One hydrolysis study was reviewed by all of the participating countries. All reported the same hydrolytic half-lives for the alpha and beta isomers of endosulfan and identified the hydrolytic product as endosulfan diol. All countries except Germany noted that the hydrolytic reaction is pH dependent. Sweden and the US noted deficiencies with the study. The US required the registrant to submit another study. This study was submitted but has not been reviewed. (Reference: Goerlitz,G.; Rutz, U. 1988).

Photodegradation in water

The one photodegradation in water study was reviewed by Sweden, Germany, and the US. The conclusion expressed in the reviews was that endosulfan is stable to photolytic degradation in water. The Swedish review noted that the study was performed according to EPA guidelines but noted two exceptions: the temperature was not kept in the recommended range; and, the mass balance determined for the dark control was not fully satisfactory. The US cited similar deficiencies regarding the variable material balances and that the intensity and wavelength of the light source were not similar to natural sunlight. The US conclusion was that the study did not fulfill the data requirement but did provide supplemental information regarding the photodegradation of alpha and beta endosulfan. A new study is required for US re-registration unless the registrant can show that the chemical does not photodegrade in an aqueous solution.

Soil metabolism

Eight studies were cited in the bibliographies reviewed in Phase 2. The review on this topic by Germany presented some conclusions on the soil metabolism of endosulfan but did not provide references. Therefore, it was not possible to determine their review of individual studies cited. Three aerobic soil metabolism studies were reviewed: two studies were reviewed by Denmark, Sweden, and the US. For one study, the same half-lives for endosulfan in silt loam and sandy loam soil were reported by Denmark and the US. Sweden did not discuss the study because it was of poor quality. The US determined that the study was not acceptable primarily because the study was terminated after 60 days and failed to establish the pattern of formation and decline of the major degradate, endosulfan sulfate. It was also noted that the calculated half-lives are questionable due to incomplete material balances. However, the study does provide supplemental information. The Denmark review noted that the study was carried out in accordance with EPA guidelines.

A second aerobic metabolism study was reviewed by Denmark, Sweden, and the US. Denmark and Sweden reported the same half-life and percentages of bound residues and both said the study was performed according to EPA guidelines. Sweden noted that the amount of recovered radioactivity was low, sampling should have been done more often, and the amount of bound residue was too high.

Germany cited a 1990 aerobic metabolism study but it was not possible to match the review statements with the study.

Two anaerobic soil metabolism studies were reviewed. Both were reviewed by Denmark, Sweden and the US. All three reviews noted deficiencies with the study. A second study was reviewed by Sweden and the US. Both reviews found the study to be adequate and reported similar results.

A combined aerobic, anaerobic, and field metabolism study was reviewed by Sweden. Results were reported for alpha, beta, and total endosulfan under the three conditions.

A degradation in soil microorganisms study was reviewed by Denmark and the US (cited by Sweden but no discussion). The results reported were that alpha and beta endosulfan oxidize to endosulfan and both hydrolyse to endodial.

One additional study of the behavior of endosulfan in soil was cited by Germany and Sweden but not discussed in either review.

Mobility and leaching

A total of four studies was reviewed on the mobility and leaching of endosulfan. One study was reviewed by Germany and Sweden. A second was reviewed by Denmark and Germany. The German review consisted of just the conclusion regarding leaching. All of the reviews for these studies concluded that the active ingredient and its metabolites do not tend to leach.

A third study was reviewed by Sweden and concluded that endosulfan was detectable 3.5 km downstream in ephemeral flow up to 3 weeks after the last application. A fourth study, reviewed by Denmark, identified two metabolites, diol and lactone, but the review stated that another test was preferred due to deficiencies.

Adsorption/desorption

Four studies on adsorption/desorption were reviewed. One study was reviewed by Germany and K_{oc} values were reported for alpha and beta endosulfan, endosulfan sulfate and endosulfan diol in various soils. A second study was reviewed by Denmark and Sweden. The results reported were the same but both countries noted problems with reviewing the study (Denmark reported an inadequate translation of the study, Sweden stated that the experimental procedure was only briefly described). A third study was reviewed by Sweden and is currently being reviewed by the US. K_{oc} values for alpha and beta endosulfan as well as endosulfan sulfate were reported for various soils. A fourth study was reviewed by Sweden and the US. The US concluded that the study did not fulfill the EPA guidelines but did provide supplemental information. Both countries concluded that endosulfan was not mobile in soil.

Extent/nature of bound residues

Five studies were cited in the bibliographies reviewed in Phase 2. One study was reviewed by the US in its 1982 Registration Standard and stated that endosulfan is degraded to endosulfan sulfate in soil. A second study dealing with the persistence and uptake by potato tubers was reviewed by Denmark, Sweden, and US. The results reported were all similar.

A third study was reviewed by Denmark and Sweden but both countries noted the poor quality of the study (US cited this study but no review was found).

A fourth study, a worldwide monitoring study, was reviewed by Sweden only although it was also cited by Denmark and Germany.

Lastly, a fifth study was cited by Germany but not discussed in the review.

Summary

The table below shows the number of studies reviewed by each country for the various environmental fate study areas.

	DK	D	S	US
Hydrolysis	1	1	1	1
Photodegradation in water	0	1	1	1
Soil metabolism	3	6	6	4
Mobility/Leaching	2	3	2	0
Adsorption/Desorption	1	1	3	2
Extent/Nature of Bound residue	2	0	2	3

3.3 Ecotoxicity

Acute toxicity - Avian

Seven studies were reviewed. The studies were done on the following species (some studies were done on more than one species):

Number of studies	Species
4	Mallard duck
2	Bobwhite quail
2	Japanese quail
1	Starling
1	Ring-necked pheasant

The results are discussed below:

a. One study on the mallard duck and one on the bobwhite quail were reviewed by all four countries. The same LD_{50} value was reported and the conclusion was that endosulfan is highly toxic to birds. The Swedish review noted that these studies were well performed. The Denmark review noted the studies were done according to EPA guidelines.

b. One study on the mallard duck was reviewed by Germany and the US. The results reported were the same.

c. One study done on the bobwhite quail, Japanese quail, and mallard duck was reviewed by Germany and Sweden. The results reported were the same. The Swedish review noted that the study was not performed according to any present guideline, the test method was poorly described, and mortality was observed at the lowest dose level in the study with the Japanese quail.

d. One study on the starling was reviewed by Germany and US and the result reported was the same.

e. One study on the mallard duck was only reviewed by Germany.

f. One study on the Japanese quail was only reviewed by Germany.

Acute dietary toxicity - Terrestrial and aquatic bird

One study on the Japanese and bobwhite quail, the ring-necked pheasant, and the mallard duck was reviewed by Germany, Sweden, and the US. The same results were reported.

Avian reproduction - Terrestrial

One study on the bobwhite quail was cited and reviewed by the US and determined to be scientifically not sound. A second study on the bobwhite quail was reviewed by all four countries and similar results were reported by each country.

Avian reproduction - Aquatic bird

Two avian reproduction studies (aquatic bird) were cited for endosulfan. One study was reviewed by Germany, Sweden and the US. The results reported by each country were similar. Sweden commented that the study was done according to guideline but noted a departure from the OECD guideline recommendation on initial ages of the birds; no NOEC was stated. US noted that the study is scientifically sound.

A second study was reviewed by Denmark and the US. Both countries noted the scientific soundness of the study but differed with regard to the conclusions regarding a NOEC. Denmark established a NOEC at 30 ppm but the US stated that statistically significant effects were noted at all dose levels and, therefore, a NOEC could not be established.

Aquatic testing: Fish acute toxicity - Warmwater species

There are at least 14 studies evaluating the acute toxicity of endosulfan to warmwater fish. The results of these studies were difficult to compare and few studies were reviewed by more than one country. The results do not vary much among the tests. Many of the tests were done on endosulfan formulated products. The German review contained a table of LC_{50} values for various fish but no references were matched with values. Also, a recent 1991

review summarized the results of many fish studies but complete references were not given for all studies. Two points are noteworthy: many different varieties of fish are studied among countries and all countries conclude that endosulfan is highly toxic to fish.

Fish acute toxicity - Coldwater species

Four studies were cited and reviewed evaluating the acute toxicity of endosulfan to coldwater fish. One study on 95.9% a.i. was reviewed by Denmark, Sweden and the US. The study results reported were the same and all noted that the study was done according to EPA guidelines. One study was reviewed only by Sweden and was done on the EC 35 formulation. Two other studies were reviewed by Sweden and the US. Sweden noted deficiencies with both studies and did not present any results. The US noted deficiencies with one study and a very old review done on the other study stated the scientific soundness of the study.

Aquatic invertebrate toxicity - Daphnia immobilization test

There are four studies that were cited and reviewed that evaluate the toxicity of endosulfan to Daphnia. One study on the a.i. was reviewed by Sweden and the US. The results presented in the reviews were the same. Two additional studies done on the EC were only reviewed by Sweden; one study was done before current guidelines existed and it was stated that one study was done according to EPA guidelines. A fourth study done on the active ingredient was reviewed by Denmark. The LC_{50} value was different from those found in the first study but it was noted that the documentation was abbreviated and the concentrations were calculated rather than measured. Conclusions were that endosulfan was highly toxic to Daphnia.

Marine/estuarine fish toxicity

Three studies were cited and reviewed that evaluate the toxicity of endosulfan to marine/estuarine fish. Two studies were reviewed only by the US: one study on the striped bass and one on the pinkfish, spotfish and striped mullet. All found LC_{50} values to be less than 1 ppb and concluded that endosulfan is highly toxic to these fish. A third study on the mosquito fish was reviewed by Germany and only the LC_{50} was included in the report.

Daphnia life cycle

There are three studies on the effects of endosulfan on the Daphnia life cycle. One study was reviewed by all four countries. The results reported were all similar. Two other studies were each reviewed by different countries, one by Denmark and one by Sweden. The results reported from all the studies were similar. For the two studies cited by Germany, it was difficult to match the results with the reference.

Chronic fish toxicity

Two studies on chronic fish toxicity were cited and reviewed. One study was only reviewed by Germany. The second study was done on the fathead minnow and was reviewed by all four countries. The results reported in the reviews were the same. Sweden considered the study invalid since survival was lower in the control than in the treated aquaria.

Honey bees

Four studies evaluating the toxicity of endosulfan to honey bees were cited and reviewed. One study was reviewed by both Germany and Sweden and similar results were reported. Each of the other three studies was reviewed by only one country. Toxicity was reported to be moderate.

Earthworm acute toxicity

Six studies were cited and reviewed that evaluate the toxicity of endosulfan to earthworms. One study was reviewed by both Germany and Denmark.

Phytotoxicity to nontarget plants

One study was reviewed by Denmark and Sweden on algae growth inhibition. The EC_{50} values reported were the same and both countries concluded that endosulfan was moderate to highly toxic to green algae.

Summary

The table below shows the number of studies reviewed by each country for the various environmental fate study areas.

	DK	D	S	US
Avian, oral	2	7	3	4
Avian, dietary	0	2	2	2
Avian, repro. terrestrial	1	1	1	2
Avian, repro. aquatic	1	1	1	2
Fish, acute warmwater	1	9	5	1
Fish, acute coldwater	1	1	4	3
Daphnia, acute	1	4	3	1
Marine, estuarine, acute	0	1	1	2
Daphnia, life cycle	2	2	2	1
Chronic fish	1	2	1	1
Honey bees	0	2	2	1
Earthworm	1	5	1	0
Phytotoxicity	1	1	1	0

4 Potential for use of reviews by other countries in lieu of conducting a separate review

This part of the report contains some judgments and also reflects the review practices and documentation practiced at this time by the US EPA Office of Pesticide Programs. The following analysis, therefore, should not be interpreted for example as a judgement on the quality and extent of the review of data by others since the data evaluation process practiced by the participating countries can not be clearly determined based on the material submitted for the Pilot Project. In some cases, resource constraints and/or a high level of trust in the primary reviewer may limit the level of documentation that countries include in a review report.

4.1 Toxicology

In the area of toxicology the citation of studies on endosulfan and the corresponding reviews are quite clear in the review reports from all participating countries. Judgements about the usefulness of any particular study are also quite uniform. The evaluation of the endpoints (NOELs, toxic signs and effects) is nearly always uniform among the countries and in agreement with the study author. The exception is the interpretation of the effects on the reproduction and development of pups. There was no disagreement in the description of effects and the level at which they occurred, but the interpretation of the meaning of these effects differed among the countries.

Since the reviews of any particular study report the same result, one could come to the conclusion that repeated review by different countries is unnecessary and just a duplication of effort. At least for endosulfan, repeated review of the same data base did not reveal any new information, beyond the information provided in the data summary by the study author. However, the identical outcome of data evaluation does not necessarily assure that the data have been evaluated by all participants in the same critical analytical fashion. In order to come to this conclusion much more would have to be known about the review process, (e.g. the analysis of individual animal data, or quality assurance checks performed by the reviewer).

Some of the shorter summary reviews (including the summary provided by the study author) would not be acceptable by US standards to fully substitute for an in-house review. US reviewers are directed to document and support major findings in their reviews by providing summary tables. For example, developmental effects must be presented in tabular form, or lower weight gains must be presented in figures and tables. Thus, the conclusions reached in the review must be documented and presented in such a fashion that the reader of the review has the evidence before him/her and can interpret its meaning independently. This high level of documentation clearly has resource implications which might limit widespread adoption of the US model.

Interpretation of the results of complex toxicological studies is often not totally clear cut. Different reviewers may give more or less weight to a marginal difference from control values, attributing borderline effects to chance or to compound administration, for example. Such differences are often best resolved through a second review of the data by a peer review group, which lends credence and confidence to the interpretation of results. None of the review packages submitted provided any insight into the internal oversight function exercised by any of the countries, although it must be assumed that the review work of an individual has to undergo some degree of secondary review by other government officials.

4.2 Environmental fate and ecotoxicity

In the area of fate and ecotoxicity, the citations of studies and the corresponding reviews are clear from Denmark, Sweden, and the US. It is somewhat difficult to match the summarized study results to the study reference in the German review. The evaluation of the endpoints is uniform across all countries.

Similar to the remarks made regarding toxicology, the reviews of any particular study report the same result.

4.3 General remarks

From the US point of view, the availability of other countries' reviews would certainly be useful in the support of the conclusion reached by the US reviewer. Similar outcomes in review would strengthen the US's own conclusion; different outcomes would give incentives to search for the reasons, or to resolve the differences.

There are certain types of studies which do not necessarily need to be reviewed by all countries. Examples of these are acute toxicity (mammalian, fish, avian, etc.) and some environmental fate laboratory studies. With regard to the acute toxicity testing, if studies were reported in a common format by the laboratory conducting the test and certified that a specific guideline was followed, then a review by one country should be sufficient.

A total replacement of US reviews (of complex studies) by other countries' reviews is at this time not a likely possibility, particularly because existing reviews are not fully transparent with regard to the review process. A one-on-one exchange and use of data review may be a possibility between a subgroup of the participating countries. In fact, Canada and the US have already shared the task of IBT study validation. In order to achieve this exchange of judgements, however, clear guidelines on evaluation procedures have to be developed so that the partners clearly understand the process and can develop trust in each other reviews. Canada and the US are at present working on a prospective effort to share data reviews of new pesticides and re-registration of wood preservatives.

5 Recommendations

The US has the following recommendations to increase mutual acceptance of other countries' data review. These recommendations should be considered as agenda items at the October workshop that is planned as part of this pilot or considered as possible unilateral or bilateral actions that could be taken by one or more countries.

1. Data reviews **of acute oral and dermal toxicity (mammalian), acute ecotoxicity (fish, avian, invertebrates), and possibly some fate laboratory studies** should be shared without a re-review of the studies. The pilot program has shown full agreement among countries with respect to the results. These studies leave no margin for "interpretation", therefore a different review outcome is literally impossible.

2. The reviews of **acute inhalation studies** possibly also could be shared without re-review. With respect to generating the air concentration of test compound, these studies are more complex and subject to interpretation. However, this is a matter of test guidelines, and since the OECD guidelines are mutually accepted, so should be interpretations of studies conducted under them.

3. The reviews of **dermal and eye irritation studies** also seem candidates for sharing. However, it might not be possible to fully adopt the interpretation of the studies, because of the descriptive nature of the "results" (e.g. "mildly irritating", "minimally irritating", "slightly irritating", "no effects on the cornea").

4. The acceptance of reviews of the more complex toxicological tests, **chronic rat, dog, and mouse study, the reproduction study and the developmental toxicity studies, environmental field testing and chronic ecotoxicity, etc.** without re-review may not be possible among all participating countries without significant work to harmonize data review procedures. However, the sharing of reviews in order to support each other's conclusions should be strongly encouraged. The ongoing re-registration process would be an excellent opportunity to share fairly complete data review packages, scientific summaries, and overall safety assessments of pesticide chemicals.

5. The review process in different countries should be further studied and made transparent to others in order to increase confidence in the adequacy and thoroughness of the reviews.

6. The formation of working groups (similar to the WHO/IPCS) should be explored in order to develop consensus building in the interpretation of study results.

7. Subgroups of member countries (2-3 countries) could be formed to explore the sharing and acceptance of each other's reviews without re-review. Exchange of reviewers among countries may assist in the acceptance and understanding of review processes.

8. As the international community seeks to implement the risk assessment recommendations of UNCED Agenda 21 Chapter 19, which call for assessing several hundred priority chemicals by the year 2000, it will be important for WHO/IPCS to work with national regulators in both the more developed and developing countries, through the newly established International Forum on Chemical Safety (IFCS) and other fora, to make the WHO/IPCS review process more transparent and ensure that it meets the needs of the user community. The Chapter 19 risk assessment recommendations will also necessitate much wider international use of national evaluations that meet agreed upon criteria. The results of this OECD Pilot Project to Compare Data Reviews will help achieve this UNCED Agenda 21 goal. A follow-up need from the pilot will be for OECD and its Member countries to interact with IFCS and IPCS to find ways to achieve wider use of national evaluations.

9. **A standardized study citation, bibliography and study review format** should be developed among the member countries, making it easier to determine which studies were in fact available and used for the health effects assessments. Reviews should clearly identify referenced studies.

Appendices

Appendix 1. COMPARISON OF RESULTS REPORTED IN COUNTRIES' DATA REVIEWS

TOXICOLOGY

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
ACUTE TOXICITY - ORAL (Values are in mg/kg.bw)									
A	Male Rats (endosulfan lactone) (Hollander, 1975)	LD_{50}	165	-	-	-	-	-	-
B	Female Rats (endosulfan lactone) (Hollander, 1975)	LD_{50}	290	-	-	-	-	-	-
C	Beagle Male Dogs (endosulfan sulfate) (Hollander, 1975)	LD_{50}	15	-	-	-	-	-	-
D	Rats (Elsea, 1957)	LD_{50}	110	-	-	110	110	110	-
E	Rats (Brancha, 1977)	LD_{50}	2850 (males) 45 (females)	-	-	-	-	-	-
F	Dog (Nogami, 1970)	LD_{50}	76	-	-	77	76.7	-	-
G	Male Sherman Rat (Scholz, 1971)	LD_{50}	-	48	-	48	48	-	-
H	Female Sherman Rat (Scholz, 1971)	LD_{50}	-	10	-	10	10	-	-
I	Male and Female Sherman Rats (Gaines, 1969)	LD_{50}	-	-	-	43	-	43 (males) 18 (females)	-
J	Male Albino Rats (4 strains) (Kretchmar, 1971)	LD_{50}	-	59-125	-	59-125	59-125	-	-
K	Male Rats (Elsea, 1958)	LD_{50}	-	86.6	-	86.6	86.6	-	-
L	Rats (Reno, 1975)	LD_{50}	-	40 (males) 9.58 (females)	-	9.66 (females)	-	40 (males) 9 (females)	-
M	Acute Toxicity (Scholz, 1971)	LD_{50}	-	-	-	25 (females)	-	-	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
ACUTE TOXICITY - ORAL (Values are in mg/kg.bw)									
N	Male and Female Wistar Rat (Diehl, 1988)	LD_{50}	-	-	100-160 (males) 22.7 (females)	22.7 (females)	-	-	-
O	Rat (Scholz, 1966)	LD_{50}	-	-	-	89 (females)	-	-	-
P	Mouse (Beta-Endosulfan) (Scholz, 1966)	LD_{50}	-	17	-	120 (female)	-	-	-
Q	Dogs (Keller, 1958)	LD_{50}	-	-	-	10 - 30	-	-	-
R	Beta-Endosulfan - Rat male/female (Diehl, 1988)	LD_{50}	-	-	-	1740 (male) 66 (female)	-	-	-
S	Beta-Endosulfan - Female Rat (Hollander, 1975)	LD_{50}	-	240	-	240	-	-	-
T	Male and Female Rat (Diehl, 1988)	LD_{50}	-	-	-	80-125 (male) 20-40 (female)	-	-	-
U	Alpha-Endosulfan - Female Rat (Hollander, 1975)	LD_{50}	-	-	-	76	-	-	-
V	Mouse Alpha-Endosulfan (Scholz, 1966)	LD_{50}	-	14	-	14 (starch) 105 (sesame oil)	-	-	-
W	Acute Toxicity (Leist, 1986)	LD_{50}	-	-	-	-	Summary of results reported under J and a.	-	-
X	Acute Toxicity (Lindquist, 1957)	LD_{50}	-	-	-	-	50	-	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
ACUTE TOXICITY - ORAL (Values are in mg/kg.bw)									
Y	Acute Toxicity (Palazzolo, 1964)	LD_{50}	-	-	-	-	-	142 (males) 53 (females) cotton-seed vehicle	-
Z	Acute Toxicity (Boyd, 1970)	LD_{50}	-	-	-	-	-	102	-
a	Female SPF Wistar Rat Alpha-Endosulfan (Hollander, 1975)	LD_{50}	-	76	-	-	-	-	-
b	Male SPF Wistar Rat (Scholz, 1977)	LD_{50}	-	106	-	-	-	-	-
c	Female SF Wistar Rat (Scholz, 1977)	LD_{50}	-	48.4	-	-	-	-	-
ACUTE TOXICITY DERMAL (Values are in mg/kg.bw)									
A	Acute Dermal - Rabbit (Females) (Gupta, 1975)	LD_{50}	-	-	-	-	167-187	182 (91% tech.) 167 (90% tech.)	-
B	Acute Dermal - Rat (Diehl, 1988)	LD_{50}	-	-	> 4000 (males) 500 (females)	500 (female)	-	-	-
C	Acute Dermal - Rabbit (Elsea, 1957)	LD_{50}	359	359	-	359	359	359 Sex not specified	-
D	Acute Dermal - Rabbit (Brancha, 1977)	LD_{50}	500-1000 (males) 1000-2000 (females)	-	-	-	-	-	-
E	Acute Dermal - Rat (Hollander, 1977)	LD_{50}	-	157	-	-	-	-	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
ACUTE TOXICITY INHALATION (Values are in mg/l.air)									
A	Acute Inhalation Toxicity - Rat (Hollander, 1983)	LC_{50}	.035 (males) .013 (females)	.035 (males) .013 (females)	.0345 (4 hours) (males) .0126 (4 hours) (females)	.0345 (males) .0126 (females)	.0345 (males) .0126 (females)	-	.0345 (males) .9126 (females) (possible typo)
B	Acute Inhalation Toxicity - Rat (Reno, 1976)	LC_{50}	-	-	-	-	-	1.16-5.66 mg/l Not acceptable because only 1 hour exposure.	-
ACUTE TOXICITY PRIMARY EYE IRRITATION									
A	Acute Eye - Rabbits (Reno, 1975)	Irrita-tion	-	No evidence of irritation of corneal damage at any time during the study	No reason to classify endosulfan as an eye irritant. Comments on validity of studies.	Slightly irritating	-	No corneal opacity occurred.	-
B	Acute Eye - Rabbits (50% endosulfan) (Makhteshim, 1982)	Irrita-tion	-	-	-	-		Not irritating to eye.	-
C	Acute Eye - Rabbits (Elsea, 1977)	Irrita-tion	Following application slight erythema and vascularization of the sclera and nictitating membrane. Eyes appeared normal by 24 h. Systemic toxicity not observed.	Inadequate for review	-	-	-	Invalid study	-
D	Acute Eye - Rabbits (Bracha, 1977)	Irrita-tion	No irritation of cornea or iris. Mild chemosis and redness of the conjunctiva in 4 animals within 24 hours which subsided at 48-72 hours.	-	-	-	-	-	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
E	Acute Eye - Rabbits (Hollander, 1977)	Irrita-tion	-	Undiluted endosulfan moderately irritating to eyes; diluted non-irritating.	-	-	-	-	-
ACUTE TOXICITY PRIMARY SKIN IRRITATION									
A	Acute Skin - Rabbits New Zealand (Reno, 1975)	Irrita-tion	-	Minimally irritating to intact skin; slightly irritating to abraded skin.	Draize Scale - The average score was .9, and therefore endosulfan cannot be considered primarily irritating.	Slightly irritating	-	Primary irritation score= .9, non-irritating	-
B	Acute Skin - Rabbits (50% endosulfan) (Makhteshim, 1982)	Irrita-tion	-	-	-	-		Not irritating to skin.	-
C	Acute Skin - Rabbits (Bracha, 1977)	Irrita-tion	(clipped intact, abraded skin); no primary skin irritation seen.	-	-	-	-	-	-
D	Acute Skin - Rabbits (Elsea, 1957)	Irrita-tion	Mild irritation.	-	-	-	-	-	-
E	Acute Skin - Rabbits Albino Himalayan (Hollander, 1977)	Irrita-tion	-	Undiluted 4/6 animals died after exposure to 500 mg; 10% solution was a slight irritant.	-	-	-	-	-
SKIN SENSITIZATION									
A	Female Pirbright - White Guinea Pigs (Jung, 1983)	Sensiti-zation	No signs of toxicity or dermal irritation seen; no skin sensitization induced.	Not a skin sensitizer	Not sensitizer, OECD guidelines however, insensitive test	Not a sensitizer	No skin sensitization properties	Not a sensitizer	Cited in bibliography but no reference in text.

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
B	Pesticide Dermatitis (Lisi, 1986)	Sensiti-zation	-	-	-	-	No data regarding endosulfan reported.	-	-
NEUROTOXICITY (Values are in mg/kg)									
A	Acute delayed neurotoxicity - hen (Roberts, 1983)	Neuro-logical toxicity	-	Not neurotoxic at 96.	Not neurotoxic at 96.	No neurotoxicity at 96.	Not neurotoxic at 96.	Not neurotox at 96. Study inadequate but not needed.	Not neurotoxic at 96.
B	Effect on rat brain acetylcholinesterase (Mullner, 1989)	Neuro-logical toxicity	-	-	-	Although a neurotoxic agent, brain AChE not affected.	-	-	-
C	Neurotoxicity in rats and mice (Gupta, 1976)	Neuro-logical toxicity	-	-	-	Cited but difficult to match results with references.	-	AChE in rat brain decreased. i.p. 30 and 60.	-
D	Neurotoxicity - rat (Ansari, 1987)	Neuro-logical toxicity	-	-	-	-	Cited in bibliography but no reference in text.	-	-
E	Neurotoxicity - pigeon (Anand, 1986)	Neuro-logical toxicity	-	-	-	-	Cited in bibliography but no reference in text.	-	-
F	Neurotoxicity - cat (Khanna, 1979)	Neuro-logical toxicity	-	-	-	-	-	No sufficient review.	-
G	Neurotoxicity - hamster and rat (Truhaut, 1974)	Neuro-logical toxicity	-	-	-	-	-	No sufficient review.	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
SUBCHRONIC TOXICITY (Values are in mg/kg.day)									
A	Repeated dose dermal - 28 days Doses: 0,1,3,9, 27, 81 (Ebert, 1985)	Dermal toxicity	NOEL = 3 Neurol. signs, convulsion, salivation	NOEL = 3 (male) NOEL = 9 (female)	NOEL = 3 (male) NOEL = 1 (female) OECD guidelines ChE inhibition Liver changes (cells)	NOEL = 9 (female) NOEL = 48 (male) "intoxication" Germany combined the review of both 28 day studies	NOEL = 3 NOEL = 9 Liver histopath; 81**?** clear toxicity.	NOEL = 3 (male & female) Liver tox. toxic shock	NOEL = 3 Liver effects; spleen weights; death at high doses.
B	Repeated dose dermal - 28 days Doses: 0,3,6,12,48 (female) Doses: 0,12,48,96,192 (male) (Ebert, 1985)	Dermal toxicity	-	NOEL = 96 (male) NOEL = 6 (female)	No NOEL was determined. Repeat study needed.	-	Effects at 12 and above. NOEL implied = 6.	NOEL = 12 (female) NOEL = 96 (male)	-
COMBINED CHRONIC TOXICITY/CARCINOGENICITY-RATS (Values are in mg/kg/day unless shown as ppm)									
A	Combined Toxicity / Carcinogenicity - rat (Ruckmann, 19??)	Cancer toxicity	Quoting JMPR report results equal to Denmark.	NOEL = 15 ppm NOEL = 0.6 Kidney tox no cancer.	NOEL = 15 ppm NOEL = 0.6 (male) NOEL = 0.7 (female) Kidney effects OECD GL good study No cancer	NOEL = 15 ppm NOEL = 0.6 (male) NOEL = 0.7 (female) MTD 75 ppm (HDT) Kidney effects - No cancer	-	NOEL = 15 ppm 0.65 LEL 75 ppm (HDT) Kidney No carcino-genicity.	NOEL = 15 ppm 0.6 (m); 0.7 (f) target organ kidney No carcino-genic effects.
B	Combined Toxicity / Carcinogenicity - rat (Keller, 1959)	Toxicity	No cancer up to 100 ppm No NOEL described; only 25 rats/dose/sex.	-	-	NOEL = 30 ppm NOEL = 1.5 Insufficient information for cancer.	No cancer to 100 ppm insufficient study not following OECD guidelines	Invalid Hazleton study	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
CHRONIC TOXICITY (Values are in mg/kg/day unless shown as ppm)									
A	Chronic Feeding - Mouse (Donaubauer, 1988)	Carcin-ogenicity	Lists JMPR review NOEL= 6 ppm 0.84 (male) 0.97 (female) organ weight changing	NOEL = 6 ppm 0.84 male No carcinogenicity Increased mortality (female)	NOEL = 6 ppm 0.84 male; 0.97 female organ weight changes No carcinogenicity	No overt effects NOEL = 6ppm 0.84 male; 0.97 female No carcinogenicity	Effects at 18 ppm NOEL not stated but implied at 6 ppm No carcino-genicity. OECD guidelines followed. GLP followed.	NOEL = 6 ppm LEL = 18 ppm Decreased survival (female) Decreased body weight (male) (No change on organ weights) Not carcino-genic	NOEL= 6ppm 0.84 (male); 0.97 (female) Decreased survival (female) Decreased liver weights No carcino-genicity
B	Chronic Feeding Mouse (NCI, 1978)	Cancer	NOEL = 0.58 (female), (male); No conclusions; mortality	-	-	Study terminated inconclusive for cancer assessment	Inconclusive for males No carcino-genicity in females	Inconclusive	Inconclusive due to early deaths in males (3.5 ppm)

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
CARCINOGENICITY - RATS									
A	Carcinogenicity - rat (NCI, 1978)	Cancer	(female) TWA 223; 445 ppm (male) TWA 408; 952 ppm No cancer females. Males not interpreted (mortality).	-	-	Doses too high invalid for cancer assessment	No conclusion for males mortality. Not carcinogenic for females. OECD guidelines not met.	-	No NOEL established No conclusion for carcinogen-icity in male rats (death) No carcinogen-icity in female rats
CHRONIC FEEDING - DOGS									
A	Chronic Feeding - dog (Keller, 1959)	Toxicity	NOEL = 30 ppm NOEL = 0.75 only 2 dogs/group/ 100 ppm Neurological signs	-	-	NOEL 0.75 Deficient "old" study	OECD guidelines not met NOEL implied = 0.75	-	-
B	Chronic Feeding - Dog (Brunk, 1989)	Toxicity	-	NOEL = 10 ppm NOEL = 0.65 (male) NOEL = 0.57 (female) Neurological signs Decreased body weight gain	NOEL = 10 ppm NOEL = 0.7 Nervous system effects	NOEL = 10 ppm NOEL = 0.65 (male); NOEL = 0.57 (female) Neurological signs, convulsion	-	NOEL = 10 ppm NOEL= 0.65 (male); NOEL= 0.57 (female) Weight gain males Neurological signs both sexes at 30 ppm (HDT)	NOEL= 10 ppm NOEL= 0.65 (male); NOEL= 0.57 (female) Neurologica l effects, neuro-muscular liver congestion.

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
C	Chronic Feeding - Dog (Baran, 1967)	Toxicity	-	-	-	NOEL= -0.75 Deficient study	-	Invalid IBT study.	-
DEVELOPMENTAL TOXICITY - RABBITS (Values are in mg/k.bw)									
A	Developmental toxicity - rabbits (Mackenzie, 1981)	Birth defects Embryo toxicity	No developmental toxicity 1.8 (HDT) Maternal NOEL= 0.7	NOEL= 0.7 No effects on pups noted at higher levels	NOEL= 0.7 (females) NOEL= 1.8 (pups) HDT NOEL= 1.8 poisoned dams, neuro-logical convulsion, etc.	NOEL= 0.7 NOEL= 1.8 hyper- activity No teratology in rabbits	No NOEL given maternal effects at 1.8 No fetotoxic/ embryo- toxic effects. OECD guidelines met.	NOEL= 0.7 NOEL= 1.8 toxic Not terato- genic in rabbits	NOEL= 0.7 (maternal) No terato- genicity

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
DEVELOPMENTAL TOXICITY - RAT (Values in mg/kg.bw)									
A	Developmental Toxicity - Rat (Mackenzie, 1980)	Devel. Toxicity	NOEL= 0.66 maternal toxicity NOEL= 2.0 (teratology) Developmental effect at 6 Note of replaced animals.	NOEL= 0.66 NOEL= 2.0 (fetotox) Decreased fetal weight. Delayed ossif. sternebrae NOEL= 6 (terat)	-	NOEL= 0.66 toxic of 2 and 6 animals replaced in high dose and control group. Not teratogenic in rat.	NOEL not stated. Implied 0.66 for dams. OECD guidelines followed. Feto/ embryotoxic effects at maternally toxic levels (skeletal effects)	NOEL= 0.66 Skeletal, visceral, external abnormalities at 6 maternal tox. Re-review (91)**?** No NOEL - misaligned sternebrae at .66	NOEL= 0.66 maternal NOEL= 2 (fetotoxic) Skeletal (sterna-brae) effects noted, however dismissed because of maternal toxicity.
B	Developmental Toxicity - Rat (Gupta, 1978)	Devel. Toxicity	-	-	-	Doses of 0, 0.5 and 10 tested, results not discussed.	Insufficient information From a literature study.	No raw data, inconclusive	-
C	Developmental Toxicity - Rat (Haley, 1972)	Devel. Toxicity	-	-	NOEL= 1.5 (HDT) IBT not sufficient for evaluation	No toxicity at 1.5 insufficient study	No conclusion (IBT)	-	-

Ref	STUDY TYPE	END POINT	AUSTRALIA	CANADA	DENMARK	GERMANY	SWEDEN	US	FAO
REPRODUCTIVE TOXICITY (Values are in mg/kg/day unless shown in ppm)									
A	Reproduction - Rat (Edwards, 1984)	Repro-duction	NOEL= 15 ppm NOEL= .75 LEL= 75 ppm litter weight decrease	NOEL= 1 reduced litter weight	NOEL= 15 ppm NOEL= 1-1.3 weight gain. Study OK but insufficient reporting	NOEL= 15 ppm NOEL= 1 litter weight decrease Histology kidney effects 75 ppm "thresh-old" effect.	OECD guidelines met. Toxic at high dose 75 ppm. No effect on reproduction, renal effect (color) noted. No NOEL given. Implied: 15 ppm (tox) 75 ppm (repro)	NOEL= 3 ppm NOEL= 0.2 for mat. tox. liver weight. NOEL for reproduction effects 15 ppm= 1. Revised by RfD committee to 15 ppm= 0.75	75 ppm= 6 Caused no effect on reproduc-tion; marginal decrease in litter weight dismissed Renal coloration noted but not considered in repro. toxicity.
B	Reproduction - Rat (Kennedy, 1965)	Repro-duction	-	-	-	NOEL= 50 ppm= 3 HDT unusable study.	-	Invalid	-

ECOLOGICAL EFFECTS

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
ECOLOGICAL EFFECTS						
ACUTE AVIAN TOXICITY (Values in mg/kg.bw)						
A	acute oral toxicity - mallard duck (Hudson, 1972)	LD_{50}	-	(by age) 27.8 @ 36 hrs. 6.5 @ 7 days 7.9 @ 30 days 34.4 @ 6 months	-	(By Age) 27.8 @ 36 hours 6.47 @ 7 days 7.89 @ 30 days 34.4 @ 6 months
B	acute oral toxicity - bobwhite quail (technical) (Roberts, 1983)	LD_{50}	42 acutely toxic	42	42 toxicity considered high	42 considered to be "highly toxic"
C	acute oral toxicity - mallard duck (technical) (Roberts, 1983)	LD_{50}	28 extremely toxic	28	28 toxicity considered to be high	28 considered to be "highly toxic"
D	acute oral toxicity - bobwhite quail (male, female) Japanese quail mallard duck (technical) (McCarthy, 1972)	LD_{50}	-	50; 56 106; 85 243; 205	50; 56 106; 85 243; 205	-
E	acute oral toxicity - starling (Schaefer, 1972)	LD_{50}	-	@ 35	-	35
F	acute oral toxicity - mallard duck Ring-necked pheasant (Hudson, 1984)	LD_{50}	-	31 80 - 320	-	-
G	acute oral toxicity - Japanese quail (male, female) (Scholz, 1971)	LD_{50}	-	159-201 in sesame oil 26-28 in starch	-	-
ACUTE AVIAN DIETARY TOXICITY - TERRESTRIAL						
A	Dietary toxicities to terrestrial birds - Japanese quail bobwhite quail Ring-necked pheasant (Hill, 1975)	LC_{50}	-	1250 mg/kg diet 805 mg/kg diet 1275 mg/kg diet	1250 ppm 805 ppm 1275 ppm slightly to moderately toxic	 805 ppm 1275 ppm

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
ACUTE AVIAN DIETARY TOXICITY - AQUATIC						
A	dietary toxicity - aquatic bird mallard duck (Hill, 1975)	LC_{50}	-	1053 ppm	1053 ppm	1053 ppm
AVIAN REPRODUCTION - TERRESTRIAL						
A	avian reproduction- bobwhite quail (Roberts, 1984)	Reproductive Effects	-	-	-	study not scientifically sound
B	avian reproduction - bobwhite quail (Beavers, 1987)	Reproductive Effects	NOEC = 60 ppm; Reproductive effects cannot be expected below 120 ppm, but at 120 ppm the percentage of cracked eggs was significantly higher than in the control group. According to EPA guideline.	NOEC = 60 mg/kg/diet equal to 6 mg/kg.bw/day. At 120 mg/kg diet feed consumption was slightly affected and 1 female produced eggs with reduced shell thickness.	No statistically significant effects correlated to treatment with exception of an increase in number of hatchlings as a percentage of live 3 week embryos. The number of cracked eggs was statistically significant at 120 ppm but was related to one pen which was related to a decrease in shell thickness.	No treatment related effects upon bobwhite exposed to 15, 30, or 60 ppm. NOEC = 60 ppm
AVIAN REPRODUCTION - AQUATIC						
A	avian reproduction - mallard duck (Beavers, 1987)	Reproductive Effects	-	NOEC = 30 mg/kg diet = 4 mg/kg/bw/day based on decreased egg production and decreased hatchability at 60 mg/kg diet.	At 60 ppm statistically significant reduction in number of eggs laid and hatchlings per hen and number of 14-day old survivors per hen. Egg shell thickness not related to treatment.	Endosulfan is expected to cause reproductive impairment for number of eggs laid, number of eggs set embryo viability, hatching success and number of 14-day old survivors at 60 ppm. The NOEC = 30 ppm.

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
B	avian reproduction - mallard duck (Roberts, 1985)'	Reproductive Effects	Endosulfan has a dose-related effect on egg-laying, percentage of cracked eggs and number of surviving 14-day young/female, which are considerably higher at 60 and 120 ppm. NOEC = 60 ppm	-	-	Statistically significant impairment of egg production occurred at all levels tested. NOEC not established. Study was scientifically sound.
AQUATIC TESTING FISH ACUTE TOXICITY - WARM WATER SPECIES						
A	acute toxicity - bluegill (Buccafuoco, 1976)	LC_{50}	-	-	-	1.7 ppb at 96 h
B	acute toxicity - bluegill (Macek, 1969)	LC_{50}	-	.0033 mg/l	-	-
C	acute toxicity - bluegill (Emulsifiable Concentrate) (Fisher, 1984)	LC_{50}	-	-	.0-.0056 mg/em. conc./liter (96 h) NOEC (96 h) = .0032 mg/em. conc./liter acute toxicity = high According to EPA guideline.	-
D	acute toxicity - Indus melanotus (golden orfe) (Emulsifiable Concentrate 35) (Knauf, 1977)	LC_{50}	-	.002 mg/l	.007 mg/for endosulfan/liter (96h) acute toxicity = high Not according to guideline.	-
E	acute toxicity - carp (Emulsifiable Concentrate 35) (Knauf, 1977)	LC_{50}	-	-	.011 mg/for endosulfan/liter (96h) acute toxicity = high Not according to guideline.	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
F	acute toxicity - carp (Emulsifiable Concentrate 35) (Knauf, 1977)	LC_{50}	.0069 mg/l Extremely toxic to carp. Method done according to BBA.	.0069 mg/l	.0069 mg/l at 96 h.	-
G	acute oral toxicity - guppy (Formulated product) (Knauf, 1978)	LC_{50}	-	-	.0052 mg/l	-
H	acute oral toxicity - Indian Major Carp (Rao, 1989)	LC_{50}	-	.0018 mg/l	-	-
I	acute oral toxicity - Channa punctata (Devi, 1981)	LC_{50}	-	.0048 mg/l	-	-
J	acute oral toxicity - Indian catfish (Singh, 1982)	LC_{50}	-	.002 mg/l	-	-
K	acute oral toxicity - Labeo Rohita (Rao, 1980)	LC_{50}	-	.001 mg/l	-	-
L	acute oral toxicity - Barbus stigma (Manoharan, 1982)	LC_{50}	-	.0043 mg/	-	-
M	acute oral toxicity - European eel (Ferrando, 1989)	LC_{50}	-	.02 mg/l	-	-
FISH ACUTE TOXICITY - COLD WATER SPECIES						
A	acute toxicity - rainbow trout (95.9% a.i.) (Fischer, 1983)	LC_{50}	.93 ug/l (96 h) Extremely toxic to rainbow trout According to EPA guideline.	Cited but difficult to match results with references.	3.67 ug/a.i./l (24 h) 1.60 ug/a.i./l (48 h) .93 ug/a.i./l (96 h) NOEC = .24 ug/a.i./l (96 h) acute toxicity = very high According to EPA guideline.	.83 ug/a.i./l @ 96 h very highly toxic (Recalculated using "moving average" method rather than "probit model")

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
B	acute toxicity - rainbow trout (Emulsifiable Concentrate 35) (Fischer, 1984)	LC_{50}	-	Cited but difficult to match results with references.	.012 mg form. endo./l (24 h) .004 mg form. endo./l (48 h) .003 mg form. endo./l (72 h) .0021 mg form. endo./l (96 h) NOEC = .001 mg/l (96 h) acute toxicity = very high According to EPA guideline.	-
C	acute toxicity - rainbow trout (86% a.i.) (U.S. EPA, 1976)	LC_{50}	-	-	Cited but not discussed because no description of performance available.	.47 ppb @ 96 hrs
D	acute toxicity - rainbow trout (Macek, 1969)	LC_{50}	-	-	Not valid study since survival in control lower than in treated.	.0032 mg/l at 6 12.7° C Supplemental data
AQUATIC INVERTEBRATE TOXICITY DAPHNIA ACUTE IMMOBILIZATION TEST						
A	Daphnia acute toxicity (99% a.i.) (Macek, 1976)	LC_{50}	-	Cited but difficult to match results with references.	0.166 mg/ai/l (48 h) acute toxicity = high (48 hour LC_{50} determined by linear regression analysis)	.166 mg/ai/l highly toxic Scientifically sound

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
B	Daphnia acute toxicity - (Emulsifiable Concentrate) (Knauf, 1976)	LC_{50}	-	Cited but difficult to match results with references.	2.03 mg/form. product/l (24 h) 0.47 mg/form. product/l (48 h) Indication that product is highly toxic. Did not follow any frequently used guidelines.	-
C	Daphnia acute toxicity (Emulsifiable Concentrate) (Fisher, 1984)	LC_{50}	-	Cited but difficult to match results with references.	.21 mg/form. product/l (24 h) .004 mg/form. product/l (48 h) NOEC (48 h) = .0001 mg/form. product/l According to EPA guideline acute toxicity = very high	-
D	Daphnia acute toxicity (active ingredient) (Knauf, 1977)	LC_{50}	LC_{50} (24 h) = 2.47 mg/l LC_{50} (48 h) = .075 mg/l concentrations not measured.	Cited but difficult to match study results with reference.	-	-
MARINE/ESTUARINE FISH ACUTE TOXICITY						
A	acute toxicity - striped bass (Korn, 1974)	LC_{50}	-	-	-	LC_{50} < 1 ppb very highly toxic

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
B	acute toxicity - fish (Schimnel, 1977)	LC_{50}	-	-	Only discusses bioaccumulation aspect of the study.	pinkfish = .3 ppb spot = .09 ppb striped mullet = .38 ppb (all at 96 hours)
C	acute toxicity - mosquito fish (Joshi, 1980)	LC_{50}	-	.008 mg/l	-	-
			DAPHNIA LIFE CYCLE			
A	Daphnia life cycle (Nebeker, 1982)	Reproduction	21 days NOEC = 20 - 75 ug/l LC_{50} (48h) = 378 - 740 ug/l EC_{50} (21 d) = 130 - 170 ug/l	Cited but difficult to match results with references.	-	-
B	Daphnia life cycle (Macek, 1976)	Reproduction	LC_{50} (48h)= 166 ug/l 2.7 < MATC < 7.00 ug/l	Cited but difficult to match results with references.	2.7 < MATC < 7.0 ug/l Not performed according to any given guideline.	2.7 < MATC < 7.0 ppb

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
C	Daphnia - 21 day Reproduction (Heusel, 1991) technical	Reproduction	-	-	LC_{50} (21 days) = .30 mg a.i./l MATC (21 days) = .063 - .20 mg/l NOEC (21 days) = .063 mg/l Done according to OECD guideline.	-
CHRONIC FISH TOXICITY						
A	chronic fish toxicity - Oncorhynchus mykiss (Knacker, 1984)	Mortality, Behavior, Growth	-	21 days NOEC = .00005 mg/l; LOEC = .00016 mg/l; LC_{50} = .000283 mg/l; NOEC = .00005 mg/l; LOEC = .00016 mg/l; No significant effect	-	-
B	chronic fish toxicity - fathead minnow (Macek, 1976)	Hatching Mortality	NOEC = .0002 mg/l (hatching) LC_{50} = .00086 mg/l	60 days NOEC = .0002 - .0004 mg/l LOEC = .0004 mg/l LC_{50} = .0008 mg/l 360 days NOEC = .0002 mg/l LOEC = .0004 mg/l	Study considered invalid since survival was lower in the control than in the treated aquaria.	LC_{50} = .0008 mg/l very highly toxic

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
BENEFICIAL INSECTS; NON-TARGET SPECIES HONEY BEES						
A	acute toxicity to honey bees (99% endosulfan) (Bock, 1986)	LD_{50}	-	-	2.58 ug/ai/bee (24 h) 2.35 ug/ai/bee (48 h) acute toxicity = moderate	-
B	acute toxicity to honey bees (Thiodan 35) (Bock, 1986)	LD_{50}	-	3 out of 10 indicated adverse effects of thiodan 35 WP.	2 out of 9 studies showed toxicity to bees; the other 7 showed no significant effects.	-
C	acute toxicity to honey bees (Schultz, 1984)	LD_{50}	-	Thiodan 35 WP is dangerous for honey bees; LD_{50} (oral) = > 10 ug/ai/bee No evidence of adverse effects on the brood.	-	-
D	acute toxicity to honey bees (Atkins, Andersen, 1967)	LC_{50}	-	-	-	4.496 mg/bee moderately toxic
EARTHWORM ACUTE TOXICITY						
A	acute toxicity - earthworms (Thiodan 35) (Hague, 1982)	LC_{50}	-	9 mg. a.i./kg at 14 days	23.9 mg/form./kg dry soil substrate acute toxicity = high	-
B	acute toxicity - earthworms (E. Foetida) (Bouche, 1984)	LC_{50}	-	7 days LC_{50} = 12 mg/ai/kg	-	-
C	acute toxicity - earthworms (E. Foetida) (Edwards, 1992)	LC_{50}	-	The active substance is assessed as "moderately toxic". LC_{50} = 1.0 - 100 mg/kg.	-	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
D	acute toxicity - earthworms (E. Foetida) (Fischer, 1990)	LC_{50}	-	7 days: LC_{50} > 18 mg/ai/kg 14 days: LC_{50} = 14 mg/ai//kg NOEC = .1 mg/ai/kg	-	-
E	acute toxicity - earthworms (E. Foetida) (Fischer, 1990)	LC_{50}	Toxic to earthworm; NOEC is based on acute toxicity 14 days: LC_{50} = 14 mg/kg/soil NOEC = .1 mg/kg/dry weight	Thiodan 35 fl: 7 days: LC_{50} = 42.3 mg/kg 14 days: LC_{50} = 30.3 mg/kg LOEC = .56 mg/kg	-	-
PHYTOXICITY TO NON-TARGET PLANTS						
A	algae, growth inhibition (Fischer, 1985)	EC_{50} Percent reduction in concentration of algae during the test period	EC_{50} (72 h) = 4.51 mg/l compared to control Extremely toxic to algae	Cited but difficult to match study results to references.	4.51 mg/ai/l (72 h) inhibitory effects were observed at concentrations above 0.56 mg/ai/l; moderate to high toxicity to green algae	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
ENVIRONMENTAL FATE						
HYDROLYSIS						
A	hydrolysis (Gorlitz, 1982)	hydrolytic half-lives	Half-lives reported same as Sweden. The hydrolysis product, endosulfan diol, is same for both isomers. Hydrolysis is slow at low pH and faster at high pH values.	Half lives reported same as listed under Sweden. Endosulfan-diol identified as the product of hydrolytic degradation.	Endosulfan-diol was only hydrolytic product of both isomers. Half-lives equal: alpha: pH5 = > 1 year pH7 = 22 days pH9 = 7 hours beta: pH5 = > 1 year pH7 = 17 days pH9 = 5.1 hours Not done in accordance with any given guidelines. Deficiencies noted.	Half-lives reported are same as listed under Sweden. Many deficiencies cited.
PHOTODEGRADATION IN WATER						
A	photodegradation (Stumpf, 1988)	-	-	Because of absent absorption > 290 nm endosulfan is not directly degraded by photolysis.	Alpha and Beta endosulfan are considered to be stable to photolytic degradation in water; photolytic half-life was greater than 1 year for the isomers. Noted that it was performed according to EPA guideline.	Endosulfan stable to photolysis in sterile aqueous solutions irradiated for 120 hours with a mercury vapor lamp. Provides supplemental information on photodegradation of alpha and beta endosulfan but does not fulfill guideline.

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
SOIL METABOLISM						
A	aerobic soil metabolism (Gildemeister, 1984)		Half-life of endosulfan was 27 days in silt loam and 18 days in loamy sand. After 60 days, 39% and 70% of the initial radioactivity remained in the two soil types. Primary metabolite = endosulfan sulfate. EPA Guideline 162-1	Cited but difficult to match reference to text.	Study was of poor quality and not discussed.	Endosulfan degraded with half-lives of 27 days in silt loam and 18 days in sandy loam soil. Major degradate = endosulfan sulfate. Study not acceptable because study was terminated after 60 days and did not establish the pattern of formation/decline of degradate.
B	aerobic soil metabolism (Stumpf, 1986)	-	Total endosulfan half-life = 110 days. Degradation of alpha endosulfan is faster than of beta. Degradation occurs through oxidation of 50 3 group to sulfate metabolites according to EPA guideline.	Cited but difficult to match reference to text.	Total endosulfan half life = 110 days, unamended soil. Mean total recovery of radioactivity for unamended and amended soil: 83-90.9%, 67.1 - 88.8%. Amount of bound residues at day 60 in unamended, amended and twice amended soil = 28.7%, 28.4%, 25.6%. Main metabolite was endosulfan-sulfate. According to EPA guideline.	Study not acceptable because it was terminated after 60 days and failed to establish the pattern formation and decline of endosulfan sulfate. Also, study done on German soil and no comparison made to U.S. soils.
C	aerobic soil metabolism (Stumpf, 1990)	-	-	Cited but difficult to match reference to text.	-	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
D	anaerobic soil metabolism (Gildemeister, 1985)	-	Primary metabolite endosulfan sulfate. Tests seems chaotic. Interesting result was that endosulfan-sulfate can be reduced back to the active compound under anaerobic conditions.	Cited but difficult to match reference to text.	Very low recovery rate and anaerobic conditions were not maintained. Results not discussed.	Not adequate study. Material balances incomplete, data too variable to assess half-life endosulfan.
E	anaerobic soil metabolism (Gildemeister, 1985) -	-	-	Cited but difficult to match reference to text.	Anaerobic half life in silt loam and sandy loam = 154 and 144 days for endosulfan; Half-life for total endosulfan was 158 and 133 days for the two soils.	^{14}C Endosulfan degraded with half-life of 144 days in sandy loam soil and 154 days in silt loam soil. Half-life of beta isomer (136-161 days); Alpha isomer (105-124 days). Endosulfan sulfate = major degradate. Satisfies data requirement.
F	behavior in soil (Gildemeister, 1982)	-	-	Cited but difficult to match reference to text.	Poor quality - not discussed.	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
G	metabolism (Stumpf, 1990)	-	-	-	DT_{50} Aerobic Alpha 12 - 40 d Beta 42 - 270 d Endosulfan 30-70 d TOTAL Endosulfan = 50 - 365 d Anaerobic Alpha 105 - 124 d Beta 136 - 161 d Endosulfan 144-154 d TOTAL Endosulfan = 133-158 d Field Alpha 46 - 70 d Beta 84 - 157 d Endosulfan 75 -100 d TOTAL Endosulfan = 140-240 d	-
MOBILITY/LEACHING						
A	leaching (Gildemeister, 1985)	leaching		The active ingredient and its metabolites do not tend to be leached.	Low mobility or immobile in tested soil types.	-
B	leaching (Gildemeister, 1983)	leaching	Mobility of metabolites can be considered low.	The active ingredient and its metabolites do not tend to be leached.	-	-

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
C	mobility (Willis, 1986)	leaching	-	-	Endosulfan was detectable 3.5 km downstream in ephemeral flow up to 3 weeks after last application.	-
D	leaching (Gildemeister, 1982)	leaching	Metabolites were found: diol and lactone. Prefer another test.	Cited but difficult to match reference to text.	-	-
ADSORPTION/DESORPTION						

A	adsorption/desorption (Stumpf, 1990)	adsorption/ desorption	-	alpha endosulfan: K_{oc} = 7800-21300;
				
				beta endosulfan: K_{oc} = 8600-13900;
				
				Sulfate: K_{oc} = 5700-11500;
				
				Diol: K_{oc} = 700-1200.
					-	-

B	adsorption/desorption (Gorlitz, 1982)	adsorption/ desorption in three soils.	Same values as reported by Sweden. Inadequate translation of study.	-	Sand 2.1 -K_{oc} = 3600±1000 Sand 2.2 -K_{oc} = 2800±800 Sandy loam 2.3 -K_{oc} = 3300±700 Difficult to evaluate since experimental procedure only briefly described.	-
C	adsorption/desorption (Gorlitz, 1987)	adsorption/ desorption properties in 4 soils; endosulfan-sulfate and endosulfan-diol.	-		K_{oc} alphha= 10161, 7969, 21347, 13684 K_{oc} beta= 11935, 13906, 8612, 12180 Alpha and beta endosulfan are expected to be immobile in soil.	Study is currently under review.

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
D	adsorption/desorption (Gorlitz, 1987)	adsorption/de-sorption properties in 4 soils: alpha and beta endosulfan.	-	-	K_{oc} Endo-sulf.= 7311, 9300, 5667, 11445 K_{oc} Endo-Diol= 994, 1122, 724, 1216 Both substances are readily absorbed in soil. Endo sulf is expected to be immobile and diol is expected to have low mobility.	Study does not fulfill guidelines but provides supplemental info. Endosulfan diol appears mobile in soil adsorption coefficient for two German soils and two U.S. soils ranged 6.2 - 32.3. Endosulfan sulfate appears to be of low mobility in soil - adsorption coefficients in two German soils and two U.S. soils ranged 45.3 - 304.4.
EXTENT/NATURE OF BOUND RESIDUES						
A	residues in soil (Stanovick, 1966)	-	-	-	-	Approximately 1 year after treatment (20 lb/ai/a) residue levels less than 1.59 ppm were found in soil samples taken at 0-6 inches. After 1 year after treatment 2 lb/ai/A) residue levels were < .05 ppm.
B	persistence/uptake by potato tubers (Stewart, 1974)	-	Values reported same as Sweden. Possible to find traces of endosulfan nearly 3 years after treatment.	-	Approximately 50% of alpha and beta endosulfan had disappeared after 60 and 800 days, respectively. Approx. residues of alpha and beta endosulfan and endosulfan and endosulfan sulfate in the soil after 700 days: .2 ppm, 1 ppm, 2 ppm	Results indicated that beta endosulfan and endosulfan sulfate are relatively persistent in soil over 2.5 year period.

Ref	STUDY TYPE	END POINT	DENMARK	GERMANY	SWEDEN	U.S.A.
C	persistence (conducted in South Africa) (Hoechst, 1983) (Conducted in India) -		Demonstrates dependency of degradation on dose level	-		No review available.
D	soil dissipation - world dissipation (conducted in Holland and Germany) (Tiirmaa, 1988)	-	-	-	Detectable amounts of both alpha and beta endosulfan after 232 days (Germany) and 257 days (Dutch). Transformation of beta isomer slower than alpha isomer.	-

Appendix 2. REFERENCES

TOXICOLOGY

ACUTE TOXICITY TESTING

Acute Oral Toxicity

A Hollander; Kramer; (8-25-1975). Acute oral toxicity in male 8PF - Wistar rats. Hoechst AG. Doc. No. A06964.
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Germany, Sweden, US, Finland, Denmark

Avian Field Testing - No studies.

Acceptance of Bait, Treated Seeds by Birds - No studies.

AQUATIC TESTING

Fish Acute Toxicity LC_{50}, Freshwater: Warm Water Species

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Marine or Estuarine Fish Acute Toxicity LC_{50}/EC_{50}

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Daphnia Life-Cycle

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Germany, Denmark

Fish reproduction and growth rate - No studies

Fish life-cycle - No studies

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Aquatic Bioavailability, Biomagnification, Bioaccumulation

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Chronic Toxicity and Reproduction with Benthic Organisms Like Chironomas

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Germany

Daphnia Reproduction (21 days)

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Germany, Sweden

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Sweden

Acute Toxicity to Honey Bees LD_{50}

A Bock (1986): Laboruntersuchungen uber die Wirkung von Thiodan 35 EC (Code: HOE 002671 OI EC33 B305) auf Die Honigbiene Apis mellifera L. Hoechst Landw. Entwichlungsabteilung. Report No. LEA-I-86-021-D. Doc. A33277.
Sweden

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Sweden

C Bock (1985): Results of Bee Toxicity Testing (Summary). Hoechst AG, Frankfurt, Germany. Rep. No. LEA-I-85-062-D. Doc. A45398.
Germany, Sweden

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Germany

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Germany

Toxicity of Residues on Foliage to Honeybees - No studies.

Acute Toxicity to Predatory, Parasitic Insects - No studies.

Field Testing for Pollinators - No studies.

Semi-Field test on Honeybees (Mortality) - No studies.

Field Test on Beneficial Anthropoids (Reproduction, Mortality, Beneficial Capacity)

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Sweden

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Sweden

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Sweden

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TERRESTRIAL VERTEBRATES

Effects on Terrestrial Vertebrates Other Than Birds - No studies.

Mammalian Field Testing - No studies.

TESTING ON OTHER NON-TARGET SPECIES

Earthworm. Acute Toxicity Test

A Hague, A.; Ebing, W. (1982): Toxicity determination of pesticides to earthworms in the soil substrate. Biologische Bundesanstalt fur land und Fonstwirtschaft, Fachgruppe fur Pflanzenschutzmitteforschung, Konigin - Luise -Strasse 19, D -1000 Berlin 33 Germany. Doc. A28776.
Germany, Sweden

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(Denmark also cited F.)

G Hague, A. & Ebing, W. (1983): Toxicity determination of pesticides to earthworms in the soil substance. - Z. Pflanzenkrankh. Pflanzenschutz, 90, 395-408.

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K Neuhauser, E. F.: Earthworms in waste and environmental management. - Academic Publishing, The Hague, Netherlands, 329-335.

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Accumulation in earthworms - No studies.

Earthworm, reproduction study - No studies.

Effects on soil microoganisms

A K.H. Domsch. Pesticide in Boden, VCH - Verlagsgesellschaft mbH, D6940, Weinheim, 1992, 128-129.
Germany

B Taubel, Baedelt, Frings (1980). Investigation of the influence of Endosulfan on the nitrification of ammonium sulphate. Hoechst AG, Frankfurt, Germany. Rep. No.21/80. Doc. A21979.
Sweden

C Taubel, Baedelt, Frings (1982): Studies of the influence of Endosulfan on the carbon cycle. Hoechst AG, Frankfurt, Germany. Rep. NO LEA/A81/029D.
DOC. A22791.
Sweden, Finland

D Taubel, Baedelt, Frings (1985): Investigation into the effect of Endosulfan technical grade a.i. on the ammonification and the nitrification of horn meal nitrogen. Hoechst AG, Frankfurt, Germany, Rep. No. LEA-A-85-030-A32668.
Denmark

Activated Sludge, Respiration Inhibition Test - No studies.

Available Data From Biological Primary Screening - No studies.

Phytoxicity to Non-Target Plants

Algae Growth Inhibition

A Fisher (1985): The effect of Endosulfan, substance, technical, identification code. HOE 002671 OI ZD95 0005 to Scenedeomus subspicatus (Green Alga) in a growth inhibition test (method OECD). Hoechst Geschaeftsbereich Landwirtschaft Pflanzenschutz Forschung Biol. Oekol.Lab, Germany Rep. No. OEK85/018E. Doc. A31389.
Sweden, Finland, Denmark

Seed Germination - No studies

Veaetative Vigor - No studies

Aquatic Plant Growth - No studies

Terrestrial Field Testing - No studies

Aquatic Field Testing - No studies

Effects on Flora and Fauna Believed to be at Risk - No studies

ENVIRONMENTAL FATE

Hydrolysis Rate including identification of metabolites and breakdown products

A Gorlitz, G.; Klockner, C. (1982) Hydrolysis of Hoe 02671 (Endosulfan):Bericht Nr. (B) 90/82; A25677. (Translation of Document No. A24433; Unpublished study received May 31, 1983 under 8340-13; prepared by Hoechst AG, W. Ger., submitted by American Hoechst Corp., Somerville, NJ; CDL:250395-C).
Denmark, Finland, Germany, Sweden, US

Photodegradation in water including identification of metabolites and breakdown products

A Stumpf, K.; Schink, C.; (1988) Photodegradation of alpha-Endosulfan (Hoe 052618) and beta-Endosulfan (Hoe 052619) in Water. Report No. CB 074/87. Hoechst AG Frankfurt/M. FRG, 11.02.88.
Germany, Sweden

Photodegradation on soil including identification of metabolites and breakdown products

A Gildemeister, H.; Jordan, H.; (1983) Photolytic Degradation of the Insecticide Endosulfan on Soil Covered Thin Layer Plates under Simulated Sunlight Bericht Nr. (B)46.83; A25805. (Unpublished study received May 31, 1983 under 8340-13; prepared by Hoechst Ag, W. Ger., submitted by American Hoechst Corp., Somerville, NJ;CDL:250395-D).
Denmark, Finland, Germany, Sweden, US

B Archer, T.E.; Nazer, I.K.; Crosby, D.G. (1972) Photodecomposition of endosulfan and related products in thin films by ultraviolet light irradiation. Journal of Agricultural and Food Chemistry 20(5):954-956.
US

C Martens, R. (1976) Degradation of [8,9,-14C] endosulfan by soil microorganisms. Applied and Environmental Microbiology 31(6):853-858.
Germany, US

D Miles, J.R.W.; Moy, P. (1979) Degradation of endosulfan and its metabolites by a mixed culture of soil microorganisms.
Finland

E McGovern, P.A.; (1988) Soil Surface Photolysis of ^{14}C-Endosulfan in Natural Sunlight. FMC Corporation FMC-323 E!388 E1, Hoechst A41608.
Denmark

Rate and route of photochemical degradation in air, identification of breakdown products

A Parlar, H. (1988) Photochemical Degradability of alpha-,beta-endosulfan and endosulfan sulphate in air. Hoechst AG, Frankfurt/M.FRG.
Germany

Soil metabolism, aerobic and anaerobic, in representative soil types

A Gildemeister, H.; Jordan, H.; (1984) Aerobic Soil Metabolism Study of the Insecticide Hoe 002671 (Endosulfan): Project No. OE134/04.02: Report No. (B)176/84. Unpublished study prepared by Hoechst AG.
Denmark, Finland, Germany, Sweden, US

B Stumpf, K.; Gildemeister, H.; Dambach, P.; von Fleischbein, I.; (1988) Hoe 002671-14C: Aerobic Metabolism of Endosulfan in Soil and the Influence of Increased Microbial Biomass. Hoechst AG, Frankfort/M., FRG.
Denmark, Germany, Sweden

C Stumpf, K.; Dambach, P.; Lens, O.; (1990) Hoe 002671-14C: Aerobic Metabolism of Endosulfan in Five Different Soils at an Application Rate of 1.3 mg/kg.
Germany

D Gildmeister, H.; (1985) Anaerobic Soil Metabolism Study with the Insecticide Endosulfan: Hoe 002671-14-C: Report No. (B)91/85. Unpublished study prepared by Hoechst AG. 24 p.
Denmark, Germany, Sweden, US

E Gildemeister, H.; Stumpf, K.; Scheinkonig, U.; Rockmann, S.; (1985) Hoe 002671-14C: Anaerobic Metabolism of Endosulfan in a Sandy Loam and Silt Loam Soil. Hoechst AG, Frankfort/M., FRG.
Germany, Sweden

F Gildemeister, H. (1982) Behavior of the active ingredient of plant treatment products in the soil. Hoechst Anal. Lab., Frankfort, Germany. Rep. No. (B)24/82. Document A37206.
Sweden

I Stumpf (1990). Hoe 002671, Endosulfan, Trade name "Thiodan" Degradation, Transformation and metabolism in soil. Hoechst Anl. Lab., Frankfurt, Germany. Report No. 0E90/109. Doc. A46012.
Sweden

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Denmark, Sweden

Biodegradation in aquatic system, aerobic and anaerobic, including identification of breakdown products and metabolites

A Gildemeister, H.; (1985) Hoe 002671-14C: Aerobic Aquatic Metabolism Study with the Insecticide Endosulfan. Hoechst AG, Frankfurt,/M. FRG.
Denmark, Finland, Germany, Sweden

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Germany

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Sweden

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Sweden

Mobility/Leaching in Representative Soil Types and Mobility of Metabolites and Breakdown Products

A Gildemeister, H.; Grundschottel, P.; (1985) Hoe 002671-14C: Leaching Study (Soil Thin Layer Chromatography). Hoechst Ag, Frankfurt/M, FRG.
Finland, Germany, Sweden

B Gildemeister, H.; Remmert, U.; (1983) Leaching Behavior of the Insecticide Endosulfan and its Degradates. Hoechst Ag, Frankfurt/M., FRG.
Denmark, Germany

C Willis, McDowell, Southwick, Smith. (1986) Methoxychlor and Endosulfan Concentrations in Unit-Source Runoff and In Channel Flow of a Complex Watershed.
Sweden

D Thier, W.; Versickerung von Thiodan 35 flussig in den Standardboden 2.1,2.2,2.3, BBA-Formblatter. Berichte (B) 55/75 1-3, Hoechst AG, Frankfurt/M., FRG, 1975.
Germany

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Denmark, Germany

F Stumpf, K.; Hoe 002671, Endosulfan, Handelsname "Thiodan" Versickerung. Bericht-Nr.: OE90/110. Hoechst AG, Frankfurt/M., FRG, 1990.
Germany

Adsorption/Desorption in Representative Soil Types Including Metabolites and Breakdown Products

A American Hoechst Corporation (1983) Adsorption/Desorption in the soil/water system.
US

B Stumpf, K.; (1990) Hoe 002671, Endosulfan, Handelsname "Thiodan" - Adsorption Desorption am Sediment. Hoechst AG, Frankfurt,/M. FRG.
Germany

C Gorlitz, G.; Koeckner, C.; (1982) Hoe 002671 Adsorption/Desorption in the Soil/Water system.
Finland, Sweden

D Gorlitz (1987). Adsorption/Desorption in the Soil/Water System. Endosulfan (Hoe 002671). Part I: Hoe 052618 (alpha-Endosulfan), Hoe 052619 (beta-Endosulfan). Hoechst Anl. Lab., Frankfurt, Germany. Rep. No. 1(76). Doc. A37591.
Sweden

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Sweden

Extent and Nature of Bound Residues in Soil

A Stanovick, R.P. (1966) Determination of Thiodan I, II and Sulphate residues in Soil: M-1898. Includes method dated June 6, 1966. (Unpublished study received April 4, 1966 under 7F0526; Submitted by FMC Corp., Philadelphia, PA.
US

B Stewart, D.K.R.; Cairns, K.G. (1974) Endosulfan Persistence in Soil and Uptake by potato tubers. Journal of Agricultural and Food Chemistry 22(6):984-986.
Denmark, Sweden, US

C American Hoechst Corporation (1983) Four published studies; Study of Gorbach, et al.; Study of van Dyk and van der Linde; Study of El Zorgani; Study of Rao and Murty.
Denmark, Germany, Sweden, US

D Tiirmaa, H.; Dorn, E.; Worldwide Monitoring of Soil Dissipation (1988). Hoechst AG, Frankfurt,/M., FRG.
Denmark, Germany, Sweden

E Tiirmaa, H.; Krebs, B.; (1989) Abbau von Endosulfan im Boden nach mehrjahriger Anwendung von Thiodan WP 50 in einer Apfelanlage. Bericht OE89/144.
Germany

Laboratory Volatility

A Archer, T.E.; Nazer, I. K.; Crosby, D.G. (1972) Photodegradation of endosulfan and related products in thin films by ultraviolet light irradiation. Journal of Agricultural and Food Chemistry 20(5):954-956.
US

B Spiro, S.; Trevisani, G.R. (1974) Studio di un metodo per la determinazione simultanea di pesticidi clorurati e fosforati nell'aria: nota 2-derivati fosforo organici e dati relativi alla cocentrazione di pesticidi nell'aatmosfera di zone agricole. [The study of a method for the simultaneous determination of chlorinated and phosphorus containing pesticides in the air: note- 2--organophosphorus derivatives and data relative to the concentration of pesticides in the atmosphere in agricultural areas.] Bulletin of the Provincial Chemical Laboratory. 25(9): 157-164.
US

C Saxena (1986) Final report. Laboratory Volatility Study of Endosulfan. Hazleton Laboratories America, Inc., Wisconsin. Doc. A34447.
Denmark, Sweden

D Beard, J.E. and Ware, G.W. (1969) Fate of Endosulfan on Plants and Grass. J. Agr. Food Chemical Vol. 17,No.2, Mar.-Apr., 1969.
Denmark, Sweden

E Strachan, W.M.J.; Huneault, H. (1979) Polychlorinated Biphenyls and Organochlorine Pesticides in Great Lakes Precipitation. Journal of Great Lakes Research 5(1):61-68.
US

Spray droplet size spectrum - No studies.

Adsorption/desorption in water

A American Hoechst Corporation (1983) Adsorption/Desorption in the Soil/Water System (Tab J-2).
US

B Gorlitz, G.; Koeckner, C.; (1982) Hoe 002671 Adsorption/Desorption in the Soil/Water System.
Denmark, Finland, Sweden

C Gorlitz, G.; (1987) Adsorption/Desorption in the Soil/Water System. Endosulfan (Hoe 002671)> Part I: Hoe 052618 (alpha-Endosulfan), Hoe 052619 (beta-Endosulfan). Hoechst Anl. Lab., Frankfurt, Germany. Rep. No. 1(76). A37591
Sweden

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Sweden

Degradation and distribution in water - sediment system - No studies.

FIELD STUDIES

Terrestrial field dissipation, distribution and dissipation in soil

A Gildemeister, H. (1983) Terrestrial Field Dissipation Studies with the Insecticide Endosulfan: Bericht Number (B) 124/83; A27207. (Unpublished study received Dec. 27, 1983 under 8340-13; prepared by Hoechst Ag, W. Ger. , submitted by American Hoechst Corp., Somerville, NJ; CDL:252043-L).
Denmark, Germany, US

B Hacker, L.A.; Endosulfan (Thiodan 35 EC) Field Dissipation Study of Terrestrial Uses on Tomatoes in Georgia/U.S.A. Hoechst Ag, Frankfurt/M., FRG.
Denmark, Germany, Sweden, US

C Mester (1987). Final report Endosulfan (LX165-03). Terrestrial/Runoff Study on Cotton in South Carolina. Landis Assoc., Inc., Placerville, California. Hoechst Anal. Lab., Frankfurt, Germany. Project No. Cr039/87. Doc.A41833.
Germany, Sweden

D Mester (1987). Final Report Endosulfan (LX165-03). Terrestrial/Runoff Study on Cotton in California with Furrow Irrigation. Landis International, Valdosta, Georgia. Hoechst Anal. Lab., Frankfurt, Germany. Proj. No. CR040/87. Doc. A42997.
Denmark, Germany, Sweden

Aquatic (sediment) field dissipation: distribution and dissipation in water

A Cornaby, B.W.; (1989) Assessment of the Fate and Effects of Endosulfan on Aquatic Ecosystems Adjacent to Agricultural Fields Planted with Tomatoes.
Germany

Forestry field dissipation - No studies.

Long term field dissipation - No studies.

High tier field studies with emphasis on Potential to leach and contaminate ground water - No studies

Spray drift field deposition - No studies.

Distribution/dissipation in air - No studies.

Accumulation in soil - No studies.

Run-off

A Mester (1987). Final report Endosulfan (LX165-03). Terrestrial/Runoff study on Cotton in South Carolina. Landis Assoc., Inc., Placerville, California. Hoechst Anal. Lab., Frankfurt, Germany. Project No. CrO39/87. Doc.A41833.
Germany, Sweden

B Mester (1987). Final Report Endosulfan (LX165-03). Terrestrial/Runoff Study on Cotton in California with Furrow Irrigation. Landis International, Valdosta, Georgia. Hoechst Anal. Lab., Frankfurt, Germany. Proj. No. CR040/87. Doc. A42997.
Germany, Sweden

Accumulation in fish

A Stumpf (1990 Summary). Hoe 00267:71, endosulfan, trade name "Thiodan", Bioaccumulation in fish. Hoechst Anal., Frankfurt, Germany. Rep. No. OE90/115. Doc. A45099.
Sweden

B Schimmel, S.C.; Patrick, J.M., Jr.; Wilson, A.J., Jr. (1977). Acute Toxicity to and Bioconcentration of Endosulfan by Estuarine Animals. Aquatic Toxicology and Hazard Evaluation. ASTM STP 634, F. L. Hamelink, Eds., American Society for Testing and Materials, 1977, pp.241-252.
Denmark, Sweden

Accumulation in other aquatic non-target organisms - No studies.

ANNEX 6

PHASE 3 REPORT

ON

IPRODIONE

Lead Country: Finland

Contents

PART 1: TOXICOLOGY

1.1 Introduction

Five countries and international organization participated in the toxicological part of iprodione Phase 3: the United States, Canada, the United Kingdom, Australia, Finland and WHO.

This Phase 3 report concerns acute toxicity, irritation, sensitization, subchronic toxicity, chronic toxicity including carcinogenicity, developmental and reproductive toxicity and metabolism on rat. The focus is on toxicological studies other than acute toxicity, irritation and sensitization.

The different areas of **toxicology** were evaluated by the different countries as follows:

- Acute toxicity:
  US, Canada, Australia, Finland, WHO
- Irritation:
  US, Canada, Australia, Finland, WHO
- Sensitization:
  Canada, Australia, Finland, WHO
- Subchronic toxicity:
  US, Canada, Australia, Finland, UK, WHO
- Longterm toxicity:
  US, Canada, Australia, Finland, WHO
- Reproductive toxicity:
  US, Canada, Australia, Finland, UK, WHO
- Metabolism:
  US, Canada, Australia, Finland, UK, WHO

1.2 Types of data reviews

1.2.1 United States

The US prepared separate reviews of different studies. Most of these reviews were made during the late 80's or at the beginning of 90's. These reviews consist of the actual **Data Evaluation Report** (DER) and the **Memorandum**. The DER is a very detailed description of the study protocol, statistical methods and results. It also contains comments of the reviewer and defines whether the study has been made according to GLP (Good Laboratory Practice) regulations and testing criteria. The length of the DER varies according

to the study in question; the longterm toxicity reviews were 20-30 pages each. The length of the Memorandum is 1-2 pages. Both DER and Memorandum include a summary of the particular study and a classification of acceptability of the study. The bibliography contains only studies that have reached the status "core classification".

After all adequate studies for the re-registration have been received and found acceptable, a **Re-registration Eligibility Document** (RED) is prepared. This document contains summaries of the toxicology, ecotoxicology and environmental fate studies that are accepted in support of the registration. The RED also contains a risk assessment and administrative measures to be taken. The re-registration process for iprodione has not yet proceeded so far that a RED could exist. (Reporter of Phase 3 is not aware whether studies that are not core classified are discussed in the RED.)

1.2.2 Canada

Canada prepared the review on iprodione in three different phases: the first part was written in 1982, the third part in 1993 and the second part between these years (year and reviewer not clearly notified). The length of this submission as a whole is 91 pages. The first and the second part are concise reviews containing available toxicological studies, the third part is prepared in a way that resembles the concept used in the US. The package also contains a separate summary of the individual studies. The Canadian review was somewhat hard to follow, because of the supplementary parts. The most recent third part, which is believed to represent the current procedure in Canada, contains rather detailed descriptions of study protocols, results and comments of the reviewer. Also the guideline used and the compliance with GLP regulations are mentioned in the most recent review. It is not clearly stated whether the evaluated studies are found acceptable. However, at some points of the third review, the reviewer concludes that "the study was satisfactorily carried out". The reviews are prepared in English.

1.2.3 United Kingdom

The United Kingdom has carried out a partial assessment of iprodione for the purpose of evaluating the risk to the consumer of eating lettuce sprayed with iprodione. The review was written in 1990. This partial assessment contains a great deal of residue data and a short evaluation of metabolism in animals, subacute toxicity, mutagenicity and teratogenicity. The review states quite briefly the protocol used and results gained. The length of the whole assessment is 19 pages, 6 of which refer to toxicology studies. The review does not contain a bibliography, summary of the toxicological studies, comments of the reviewer, statement of the acceptability of the studies, information on following GLP regulations or test guidelines. Afterwards a bibliography was requested by the reporter of this Phase 3 work. However, the bibliography was totally different when compared to the other bibliographies submitted, though it is obvious that most of the studies evaluated by the UK were also evaluated by some other country. The difference was due to the fact that the bibliography submitted by the UK listed studies after May & Baker codes and afterwards it transpired that Rhone Poulenc Ltd deals with the majority of May & Baker’s work.

1.2.4 Australia

Australia prepared the toxicological evaluation of iprodione very recently in February 1994. The review is written in English and its length is 50 pages including appendices. The review has a very large consolidated summary and discussion. The review covers all fields of toxicological studies, describing the study protocol rather briefly and the results in more detail. The review does not mention whether the studies have been made according to a test guideline or GLP regulations or whether the studies were accepted for re-registration. The review gives an ADI-value based on the studies reviewed.

(Comment from Australia: the Australian report is a considered report, and thus usually only studies that do not meet requirements or are in any way deficient are described in detail. The absence of such a statement reflects the acceptance of the study protocol. Australia, whilst requiring GLP for toxicology studies does consider non-GLP studies on their merits and will include these studies in the report if they are assessed as valid. Similarly recognised test guideline standards (OECD, US, Japan) are accepted. As a direct outcome of the OECD Pilot Project, Australia has initiated from March 1994 the inclusion of study protocol information and GLP status in its reviews.)

1.2.5 Finland

The Finnish review covers all fields of toxicological studies. The Finnish evaluation of iprodione was prepared for Nordic co-operation in 1991 and thus it was written in English. The length of the review is 38 pages including appendices. The review contains a summary and conclusions which are, however, much shorter than in the Australian review. Also the study protocol is described rather briefly, but the results in more detail. Separate comments of the reviewer are not included. GLP has not been taken into account and the evaluation contains only a general statement "The studies follow broadly the OECD guidelines for the testing of chemicals", meaning in practice that the studies are accepted to support the re-registration of iprodione. An ADI value was discussed in this Nordic review.

(Comment from Finland: more attention will be paid to the GLP requirements and test guidelines in the review process. Such remarks will be included in the reviews.)

1.2.6 WHO

The draft review of iprodione made in 1992 was used in this Phase 3 work. The draft review was compiled for the FAO/WHO Meeting on Pesticide Residues (JMPR). The review is written in English and consists of 19 pages including a bibliography. The WHO review is presented in much the same way as the Australian and Finnish reviews. The review covers different fields of toxicological studies describing study protocols very briefly and results in more detail, but is more concise than the Australian or Finnish evaluations. The Guidelines for the Preparation of Working Papers for the WHO Expert Group on Pesticide Residues (Geneva, November 1991, received afterwards) states that studies that are used for setting the ADI or otherwise used for making a determination of safety should be summarized in more detail than those that are peripheral to the safety evaluation, i.e. those that are of limited design or are of minor importance. This discrimination was not, however, very evident in the review of iprodione.

There is no comment on the acceptance of the studies and whether the studies have been carried out according to a test guideline or GLP regulations. There is a separate heading "studies which will provide information valuable in the continued evaluation of the compound". The WHO review also contains a summary with comments, a listing of dosing levels causing no toxicological effect and an ADI-value based on the studies reviewed.

1.2.7 Comparison of the data review types

The reviews that most resembled each other were the Australian, Finnish and WHO reviews. The review of the US is much more thorough-going, treating each separate study in detail. However, the final Re-registration Eligibility Report would resemble the length and content of the reviews made by Australia, Finland and WHO. It seems that the Canadian evaluation procedure is moving towards the procedure used in the US, but on the basis of the supplemental evaluation of iprodione it is hard to draw final conclusions. The review made by the United Kingdom is much shorter and more concise than the other reviews evaluated.

The most obvious difference between the reviews made by the US and others is that only the US categorically and clearly identifies:

- the test guideline used and discrepancies in following it,
- comments on test substance homogeneity and stability,
- comments on statistical analysis,
- comments on following the GLP regulations,
- statement of the acceptability of the study for the registration purpose.

The impression is that the other countries have accepted all the studies submitted, or otherwise that the totally unacceptable studies are not included in the review at all. Rejection of the studies does not, however, seem probable, because of the limited number of iprodione studies. Quite frequently equivalent studies were reviewed except for the very recent long term studies, which were available after 1992 and reviewed only by the US and Australia.

The comprehensiveness of the evaluations also varies. Reading the review of the US is time consuming, because of the separate study evaluations. Thus it is also difficult to draw an overall conclusion on the toxicological profile. However, one must bear in mind that the purpose of these separate reviews is to build the basis for a RED, which includes a summary and conclusions.

The dose levels are usually expressed both as ppm (mg/kg in diet) and mg/kg/d. However, the reviewers should be very careful not to confuse these units of measure.

Sometimes different reviews refer to the same end point as a NOAEL (no-observed-adverse-effect-level) or NOEL (no-observed-effect-level) value. Especially WHO seems to prefer the use of NOAEL rather than NOEL values.

Usually the animal strain used is mentioned, but not always.

Interestingly Australia uses the expression "examination is unremarkable" meaning that the examination (for example biochemistry) showed no treatment-related effects of any biological significance.

The most heterogenous use of terminology was in the developmental and reproductive toxicity studies. However, in the reviews of teratogenicity studies there was no overlap in the use of the terms malformation or variation. (Iprodione is not a good model substance to compare interpretation of malformations or variations, because it has no teratogenic potential.) The greatest differences were seen in the definition of maternal toxicity and perhaps also of fetal toxicity. In some reviews the terms developmental toxicity and teratogenicity as well as embryotoxicity, fetotoxicity and embryofetal toxicity were used as equivalent end points. In reproductive toxicity studies it is also sometimes unclear what is meant by endpoint parental toxicity, embryofetal toxicity or reproduction toxicity.

1.3 Comparison of values/results reported in the data reviews

1.3.1 Overlap of the studies

In the reviews excluding residue studies, altogether 57 different toxicological studies were cited. **None** of the studies were cited **by all** (6) or 5 of the countries participating in this project. About 18% of the studies were cited by 4 countries, 23% by 3 countries, 30% by 2 countries and 16% by only one country.

For the Phase 3, 39 studies were selected for comparison in table form. Metabolic studies performed with species other than rat, subacute (reviewed only by WHO) and mutagenicity studies were not included. The FAO review of the metabolism part was not used, because it seemed that the summaries of the FAO review were taken from some other source than the original metabolism studies.

1.3.2 Reference lists

It occurred that sometimes the bibliographies of reviews listed studies that were not cited in the review, or vice versa, the review included studies that were not mentioned in the bibliography. This was noted especially in the Finnish review. Also quite often the same study was cited differently; the name/names of the study author/authors and the year varied. Finally the report number, if mentioned in the bibliography, revealed that the study was in fact the same as in another review. It seemed that especially Canada had a divergent style of listing the studies.

The bibliography received from the US during Phase 2 included only 5 citations. Further information about studies that were not accepted was requested afterwards. It appeared that many of the studies that were first found unacceptable were classified as accepted (core classification) or supplemental after receiving further clarification from the applicant. For the time being it is not certain whether these studies are already included in the bibliography.

At least in the case of the partial assessment of iprodione by the UK, no reference list was attached. After a request a reference list was obtained, but it was found to be very different from the other bibliographies (see 1.2.3).

1.3.3 Test areas, studies addressed

Acute toxicity studies

WHO, Finland and Australia gave the acute toxicity end points (LD_{50}) in table form. However, the Finnish evaluation also briefly described clinical symptoms.

In most cases when the same study was evaluated by more than one country, the end point (LD_{50}/LC_{50}) was the same. However, in ref. 2 WHO very generally states that the LD_{50} value is above 2000 mg/kg and the US gives specific values. Sometimes it is not clear, possibly by mistake, whether the LD_{50} **is** the tested dose or **above** it (see ref. 4). It seems that in acute inhalation toxicity studies more attention should be paid to the particle size analysis and the aerosol producing method in addition to the end point and clinical symptoms.

Irritation and sensitization studies

In all reviews the same conclusions were drawn in irritation and sensitization studies. However, it is not clear which scoring or classification systems different countries used for placing chemicals in irritation or sensitization categories. (Finland uses the European Union classification system; directives 67/548/EEC for chemical substances and 88/379/EEC for preparations. Australia submitted afterwards pages from a guideline document for evaluators concerning their own descriptive terms for acute toxicity, which is attached in Appendix 3.)

Subchronic and chronic toxicity studies including carcinogenicity

- Differences in NOEL values:

Ref. 18 (5 months in diet/rat): according to the UK and Australia there were no treatment-related effects and thus the NOEL was the highest dose level, 1000 ppm. According to Canada and Finland the body weight gain and food consumption were reduced at and above the 500 ppm dose level and thus the NOEL was considered to be 150 ppm. Canada states additionally that the NOAEL was 500 ppm due to unpalatability of the diet.

Ref. 20 (3 months in diet/dog): the NOEL was 2400 ppm according to Canada, the UK and Australia, while according to Finland it was 800 ppm. In the Finnish evaluation the LDH activity was considered to be increased already at 2400 ppm dose level and congestion of the mesenteric lymph nodes was seen in all dogs of the 2400 ppm dose group. Both the UK and Finland considered that at the highest dose (2400 ppm) there was an anaemic tendency, while Australia stated "haematology examination was unremarkable".

Ref. 23 (52 weeks in diet/dog): all countries agreed on NOEL values. All countries also noted retinal hyperreflection at the higher doses, but only the US and Australia clearly stated that this was not a toxicological effect. On the contrary Canada stated that it was progressive retinal atrophy.

Ref. 28 (52 weeks in diet/dog): a supplementary dog study was evaluated by WHO, the US and Australia. In the Australian review it was not made clear that this study had only a supplementary role and thus not all parameters were studied. According to WHO and the US the NOAEL/NOEL was 400 ppm because of the decrease in female erythrocyte parameters. According to Australia the NOAEL was the highest dose 600 ppm, because the erythrocyte parameters were reduced occasionally and not in a dose-related manner, and they were comparable to those of controls at week 52.

Ref. 26 (Chronic and carcinogenic study in mice): according to Australia the NOEL was the highest tested dose level, 1250 ppm. Australia did not comment achieving maximum tolerated dose (MTD). Because of the reduced relative organ weights Canada set the NOEL at 500 ppm and Finland at 200 ppm. All countries agreed that there was no increase in the incidence of tumors.

Ref. 24 (Tumorigenic and toxic effects in rat): at first the US considered that this study had no NOEL, since 150 ppm produced vacuolation of zona reticularis of the adrenal gland. After receiving the historical control data this lesion was considered to be comparable to the mean of the control data. In the Australian review there is a table in which generalised fine vacuolation of zona reticularis in males was statistically significantly increased ($p < 0.05$) at 150 ppm and ($p < 0.01$) at 300 and 1600 ppm. However, there was no comment in the text as to why this effect at the lowest dose was not considered a toxicologically significant effect. Finally both the US and Australia considered that the NOEL was the lowest dose, 150 ppm.

- Evaluation of carcinogenicity:

All countries seemed to agree on the findings of the carcinogenicity studies. However, some countries prefer to talk about tumorigenic/carcinogenic potential, others about malignant or benign tumors or others about neoplastic lesions. Comparison of the results of the carcinogenicity evaluations was difficult due to the fact that the most recent carcinogenicity studies, which reported findings of tumorigenicity, were reviewed only by the US and Australia. Below are different countries' conclusions about the results of individual carcinogenicity studies.

* mouse, 1975 (ref. 26):
  - "no evidence of tumorigenic or carcinogenic potential" (Canada)
  - "no increase in occurrence of malignant tumors, but number of mammary glands and thymus examined were few" (Finland)
  - "the distribution of the neoplastic and non-neoplastic lesions do not appear to be treatment-related" (Australia)

* mouse, 1993 (ref. 25)
  - "at 4000 ppm benign and malignant liver tumors and benign ovarian luteomas were noted" (US and Australia)
  - "Iprodione has carcinogenic potential" (US)

* rat, 1976 (ref. 27)
  - "no evidence of tumorigenic or carcinogenic potential" (Canada)
  - "no increase in occurrence of malignant tumors" (Finland)
  - "no treatment relationship of neoplastic and non-neoplastic findings" (Australia)

* rat, 1992 (ref. 24)
  - "at 1600 ppm benign testicular tumors were increased, which also showed a statistically significant dose-related trend" (US)
  - "at 1600 ppm benign testicular tumors were increased and the incidence was well above the incidence in historical controls" (Australia).

• General remarks

WHO does not always seem to report biochemical, haematological or urinalysis changes. Sometimes it was only mentioned generally that there were microscopic findings in some organs, not describing what type of findings.

WHO and Canada consider a one-year dog study to be a subchronic study while the US and Australia consider it to be a chronic study. In the Finnish review of iprodione, the one-year dog study was not submitted for evaluation, but otherwise it has been debated whether the one-year dog study should be considered a subchronic or a chronic study. According to the OECD Test Guideline 409 (Subchronic Oral Toxicity - Non-rodent: 90 day Study) a subchronic oral study is the administration of the repeated oral dosing of a chemical to experimental animals for part (not exceeding 10%) of a life span. According to the OECD test guideline 452 (Chronic Toxicity Studies) the duration of the exposure in a chronic study should be at least 12 months.

Doses expressed as mg/kg/d varied slightly in the reviews. However, in some studies, due to unpalatability, the consumption of the active ingredient can vary considerably during the study, and this was not always mentioned.

Developmental toxicity and reproduction studies

Ref. 35, Teratogenicity; rat, oral: countries agree on effects and on the NOEL values in this study. However, the NOEL/NOAEL (90 mg/kg/d) is set for embryofetal toxicity in the WHO evaluation, for embryotoxicity in the Finnish evaluation, for developmental toxicity in the US evaluation and for fetotoxicity in the Canadian evaluation. This same terminology was also used in evaluation ref. 33.

Ref. 30, Teratogenicity; rat, oral: according to the US and Australia the NOEL for maternal toxicity is 200 mg/kg/d, but according to Finland and the UK the NOEL value for maternal toxicity cannot be set, because the body weight of the dams was decreased at all dose levels. In the US evaluation NOEL was 200 mg/kg/d for fetal toxicity and $\geq$ 400 mg/kg/d for teratogenic effects, but in the Australian evaluation NOEL was 400 mg/kg/d for developmental effects. The UK's opinion confirms with Australia that there is no evidence of fetotoxicity or teratogenicity. Finland noted that at the 400 mg/kg/d dose level sites of implantation were reduced and the NOEL for teratogenicity was 400 mg/kg/d.

Ref. 29, Teratogenicity; rabbit, oral: in the evaluation by the US and Australia, a NOEL for maternal toxicity could not be demonstrated, because the body weight gain was reduced at all dose levels. In the Finnish evaluation, it was admitted that at 200 mg/kg/d dose level the food consumption and body weight gain were reduced (slightly, not statistically significantly), but the NOEL for maternal toxicity was set at 200 mg/kg/d. The same applies for the evaluation by the UK, but the NOEL was set at 100 mg/kg/d. Finland, the UK and Australia agree that the NOEL for embryo- or fetotoxicity was 100 mg/kg/d. The US review suggests that no NOEL value exists, because there was a dose-dependent increase in the amount of resorptions, decrease in fetal birth weight and a dose-dependent increase in ossification retardation, which was statistically significant, even at the lowest dose. Furthermore the US classifies this study only as supplemental, because dosing did not encompass the entire period of major organogenesis.

Ref. 32, 2-generation reproduction: WHO and the US agree on the NOAEL/NOEL value for pups (1000 ppm), but WHO describes it as a NOAEL for embryofetal toxicity and the US as a NOEL for reproductive toxicity. At the higher dose level clinical signs were observed, reduced viability of the pups and decreased pup weight.

Metabolism studies

The way of evaluating metabolism studies was rather consistent, but there were naturally differences in the number of details. Inclusion of metabolic schemes would be informative. Usually the extent of absorption, distribution, biotransformation and elimination was comparable in the different reviews. However, the US did not accept the rat metabolism study (ref. 36), since HPLC and TLC failed to identify at least 2 major metabolites and up to 22% of the urinary radioactivity and up to 88% of the fecal radioactivity. No comments on the acceptability of this study were given by WHO or Canada.

1.3.4 Conclusions parts of the reviews

The toxicological profile and effects seen in the studies were briefly summarized in the conclusions part of the Finnish evaluation. The lowest NOEL was determined (7 mg/kg/d) and ADI concluded to be 0.07 mg/kg b.w./d. The ADI value was based on the 5 month rat study (The ADI value is not normally included in the review report in Finland). The one-year dog studies were not submitted to Finland.

In the WHO review the toxicological effects were also briefly summarized, stating critical NOEL levels of different studies. WHO has classified iprodione as unlikely to present an acute hazard in normal use. The former ADI (0 - 0.3 mg/kg b.w./d) is based on a multi-generation reproduction study was revised. The new ADI (0 - 0.2 mg/kg b.w./d) based on the results of several studies including the reproduction study in rats, the teratology study in rabbits, and the one-year study in dogs. A safety factor of 100 was applied to the NOAELs from these studies.

The UK review does not include conclusions about the toxicological studies. Instead the rewiew includes a section on consumer exposure, evaluating the highest likely intake of lettuce, the highest likely residue in lettuce and the highest likely intake of iprodione residues. The ADI value set by WHO in 1977 (0 - 0.3 mg/kg b.w./d) was applied and the theoretical maximum intake was calculated to be well within the ADI value.

In the review by Canada only separate study summaries were included, but no overall summary or conclusions. The lowest accepted NOEL or the possible ADI value were not presented.

Also in the reviews by the US, only separate study summaries were included. Based on the old one-year dog study (1984), a RfD (reference dose = acceptable daily intake) of 0.04 mg/kg/d was established. The registrant performed a new supplementary one-year dog study in 1991, which was found acceptable in combination with the study performed in 1984. In the new study and when combining these two studies, the NOEL is 400 ppm which corresponds to 18 mg/kg/d. On this basis the current RfD will be reconsidered. These dog studies were not evaluated by Finland or the UK. There was no discussion of the possible tumorigenic potential, but there was a mention that the carcinogenicity reviews will be sent to the HED Cancer Peer Review Committee for acceptance.

The Australian evaluation contains a consolidated summary of the toxicological studies performed and also a very extensive discussion part concentrating mostly on observed carcinogenic potential in the new studies (evaluated only by Australia and the US) and the possible mechanism causing it. "Iprodione was tumorigenic in rodents at the maximum tolerated dose only, and in the case of luteomas, the incidence of these tumors (5/50) varied little from the testing facility's historical control data (0/52 - 4/50) from 8 studies. Coupled with the lack of positive genotoxicity findings, the above results suggest that iprodione is not a genotoxic carcinogen in rodents, but that tumors are possibly due to a perturbation of sex hormone regulation, particularly in the case of testicular and ovarian tumors. The presumed potential of iprodione is to competitively antagonise binding to steroid hormone receptors. The tumor distribution and pattern seen in rodents at the MTD are consistent with such a hypothesis. Further support for the mechanism of action involving perturbation of sex hormone regulation at very high doses (and not via a tumor promoting activity) comes from a number of other findings. Structurally related drugs (flutamide) showing similar animal tumors have not been found to be tumorigenic in humans and clear NOELs have been established. Secondly, Leydig cell tumors occur at a very low incidence in humans (< 1%) and there is evidence that humans may be less susceptible to the development of testicular tumors than rats." A NOEL of 4 mg/kg/d, established from the one-year dog study, was used to estimate ADI. A 100-fold safety factor was chosen, giving an estimated ADI for humans of 0.04 mg/kg/d. It is notable that although a NOEL as high as 600 ppm was established in the supplemental one-year dog study (ref. 28), the lower NOEL (100 ppm) from the actual one-year dog study was used in the establishment of the ADI value. The justification for this choice was not discussed.

1.4 Potential for use of reviews by other countries in lieu of conducting a separate review

It seems that for the time being countries are not entirely ready to use each other's reviews for pesticide registration in place of actually conducting a national data review. Based on this Pilot Project work, the level of detail in the reviews varies, bibliographies and citations can be misleading, transparency is lacking, acceptance of the studies is not always clearly considered, the basis for setting a NOEL is not always clear, the practice of using historical controls needs more guidance, and terminology is in some cases inconsistent. An additional factor which also lessens the possibility of using the reviews, is the fact that the set of

evaluated studies varies. This is not, however, the fault of the reviewer but of the applicant, who does not submit the same set of studies to all countries.

These impediments could, however, be solved with international co-operation, some of them with ease. The progress of the evaluation procedure to include active substances in Annex I of the European Union Plant Protection Product Directive should be used to achieve this goal, and the OECD Pesticide Forum work should be deepened in this context.

Speaking for Finland, the toxicological reviews made by US-EPA could in fact be used to a great extent as a basis for the registration and for producing the statement of the health effects, since this Pilot Project has shown that US-EPA conducts the reviews with great attention to detail and thoroughness. The problem is that producing the final RED is a lengthy process and the desired review is not necessarily available. Also the reviews made by Australia and WHO could be used to a great extent. For Finland there is no legal obstruction to use of an evaluation made by another country.

On the contrary, it seems that for the US partly due to legal reasons, it would be impossible to use evaluations made by other countries in lieu of conducting a separate review. However, the evaluation made by Canada ("the third review") could possibly be used by the US as supportive material.

In Australia recent changes in pesticide legislation have established a strong public consultation element to the evaluation process including the need for transparency in decision making with respect to hazard assessment. Because the basis for the decision is not usually provided in the overseas assessments, the use of such assessments may not be practical under such constraints.

As a conclusion it seems that the European and Australian vs. North-American ways of conducting toxicological hazard assessment are rather different, although the overall conclusion on the hazard does not seem to be conflicting in this case.

In many cases there is a potential for using reviews made by other countries to support a country's own data review or parts of it. However, it seems that confirmation of the NOEL values needs to be reconsidered. At least the existing reviews can provide:

- a means of comparing whether any data exist that have not been submitted,

- an overview of the potential major toxicological problems and possibly decisions taken,

- a means of shortening the time taken to assess, for example, acute toxicity data, whilst allowing more time to concentrate on the assessment of pivotal studies.

The potential for using reviews should be considered together with the information on the process of conducting a toxicological review in different countries. Peer review processes would, of course, increase the potential for using reviews.

1.5 Recommendations

Finland makes the following recommendations to increase the possibility to use future assessments instead of conducting a separate assessment:

1.5.1 Technical recommendations

• OECD could design a model bibliography. A decision should be made regarding what date is used in the bibliography; whether it is the study performance termination day, or the date the report was written or accepted in the laboratory. It should also be considered, whether the study is identified by the testing laboratory or/and the persons who wrote the report.

• OECD could design a format for an evaluation describing all details that must be included. This format or working paper pattern could include:

- titles and headings
- minimum requirements for description of details of protocol and results (i.e. strain used, number of animals, purity of the chemical, vehicle etc.)
- compliance with GLP regulations
- compliance with generally accepted test guidelines (If the study is conducted in accordance with a generally accepted test guideline there is usually no need to describe the study performance in detail.)
- comments of the reviewer; comments proved to be very useful increasing transparency and reliability of the review
- additional studies required (might be difficult to include in the review, since in many countries the review and other administrative measures are separate).

• The OECD Secretariat has already compiled a document of the review-conducting process in different countries. This document should be updated in the future and it should be verified that this document is sufficiently transparent.

• The idea suggested by Switzerland of a clearinghouse for creating a data base of the studies performed with pesticidal active ingredients is worthy of support.

1.5.2 Scientific subject related recommendations

• Although it is usually the case that concurrent controls of the test must be used in the consideration of statistical significance, in some cases the historical control data might be informative. There is a need for guideline or criteria regarding what kind of historical control data are acceptable to use instead of the concurrent controls. Such a guideline should also note that historical control data change with time, and that the age of the experimental animals during measurements of different parameters is not insignificant.

• A common basis for setting a NOEL value should be created. Special attention should be paid to absolute and relative weight changes of organs, body weight or body weight gain change. The effects of a dose-dependent trend vs a positive trend

which is not dose-related should be discussed for their significance. Also the difference between NOEL and NOAEL values should be discussed.

• The terminology used to describe teratology, developmental toxicity and reproductive toxicity needs clarification. Special attention should be paid to maternal toxicity. In conjunction with the consideration of the NOEL value, it should be defined how great the body weight reduction or body weight gain reduction must be before it can be considered as maternal toxicity.

It would be practical to carry out recommendations that are found worthy of support in different steps. The technical issues are probably easier to solve than the scientific ones.

Appendices on toxicology

Appendix 1. REFERENCES

This bibliography is organized by study type in **toxicology**. Within each section the studies are listed alphabetically. Under each study citation is a list of those countries which reviewed the study. The reference number on the left is the same as in the table comparing different studies.

ACUTE TOXICITY

ORAL

1. Babish, J.C. (1976). Acute oral toxicity in rats. Food and Drug Research Laboratories, US.
   WHO, Australia

2. Cummins, H.(1989). Iprodione: Acute oral toxicity study in the rat. Project number RHA/255: 89/RHA255/0391. Life Science Research Ltd.
   WHO, US

3. Pasquet, J. & Mazuret, A.(1973). Acute oral toxicity in mice. Study no 17309.
   Canada

4. Pasquet, J. & Mazuret, A.(1974). 26019 RP:Acute toxicity and local tolerance. Report SUCRP-DSPh 17746 from Rhone-Poulenc, France. (mouse/oral; rat/oral, dermal; rabbit/dermal; dog/oral)
   WHO, Finland, Canada, Australia

5. Takehara et.al.(1976). Acute oral toxicity of Rovral (RP 26019). I. Oral, intraperitoneal and subcutaneous administrations in rats. 4th Research Department Nippon Institute for Biological Science.
   WHO, Finland

6. Takehera et.al.(1976). Acute toxicity of Rovral (RP 26019). II. Oral, intraperitoneal and subcutaneous administrations in mice. 4th Research Department Nippon Institute for Biological Science.
   WHO, Finland

DERMAL

7. Babish, J.C.(1976). Acute dermal toxicity in rabbits. Food and Drug Research Laboratories, US.
   WHO, Australia

8. Plutnick, R.P & Kapp, R.W.(1988). Iprodione (technical) -acute dermal limit test in the rabbit. Report 209806 from Exxon Biomedical Sciencies, US.
WHO

4. see the combined study under heading "oral"

INHALATION

9. Coombs, D.W. & Clark, G.C.(1977). RP 26019 technical: acute inhalation toxicity-four hour LC_{50} in rats. Report RNP 75/775 from Huntingdon Research Centre Ltd., England.
WHO, Canada, Australia, Finland

INTRAPERITONEAL

5. see the combined study under heading "oral"

6. see the combined study under heading "oral"

SUBCUTANEOUS

5. see the combined study under heading "oral"

6. see the combined study under heading "oral"

IRRITATION/DERMAL

10. Babish (1976). Primary skin irritation study with rabbits. FDRL. Waverly Research Center, US.
WHO, Finland, Australia

11. Bonnette, K. (1991). Primary skin irritation study in rabbits with iprodione: Final report 3147.108. Springborn Laboratories, Inc.
WHO, US, Canada

4. see the combined study under heading "oral"

IRRITATION/EYE

12. Babish (1976). Eye irritation test in rabbits. FDRL. Waverly Research Center, US.
WHO, Finland, Australia

13. Bonnette, K. (1991). Primary eye irritation study in rabbits with iprodione: Final report 3147/109. Springborn Laboratories, Inc.
WHO, US

4. see the combined study under heading "oral"

SENSITIZATION

14. Trimmer, G.W.(1988). Iprodione (technical)-dermal sensitization test in the guinea-pig (Buehler method). Report 209821 from Exxon Biomedical Sciences, Inc, US.
WHO, Finland, Canada

15. Pasquet, J.& Mazuret, A.(1976). 26019 RP Skin sensitization study in the guinea pig. Report 18918. 6 December 1976.
Australia, Finland

SUBCHRONIC TOXICITY

16. Fryer, S.E.(1990). Iprodione: subacute toxicity to mice by dietary administration for 13 weeks. Report RNP 323/90667 from Huntingdon Research Centre Ltd, England.
WHO

17. Fryer, S.E. (1990). Iprodione: subacute toxicity to rats by dietary administration for 13 weeks. Report RNP 322/90767 from Huntingdon Research Centre Ltd, England.
WHO

18. Ganter et.al. (1973). 5 month oral toxicity in the rat in comparison with dichlozoline (Sumitomo trade name Sclex=23319 RP). SUCRP Ph no 17124.
Finland, Canada, Australia, UK

19. Ganter et.al.(1977). 26019 RP: Subacute percutaneous toxicity study (3 weeks) in the rabbit. RP/RD/CNG No 19300. 20 September 1977.
Australia

20. Ganter & Girad (1979). 3 month oral toxicity of 26019 RP orally in the dog. Centre de Recherche et d'Elevage des Oncins. Project 731008.
Finland, UK, Canada (marked: November 1973, authors J.Beurlet and M. Goldman; but probably is the same study)

21. Itabashi et al.(1978). Three-month dietary oral toxicity study of 26019 RP in rats. Nippon Institute of Biological Sciences.
WHO, Finland

22. Siglin, J. (1991). 21-day dermal toxicity study in rabbits with iprodione technical: Final report 3147.107. Springborn Laboratories, Inc.
US, Canada

CHRONIC TOXICITY AND COMBINED STUDIES

23. Broadmeadow, A. (1984). Iprodione: 52-week toxicity study in dietary administration to beagle dogs. Report 84/RH0022/179 from Life Science Research, England.
WHO, Canada, US, Australia

24. Chambers, P.R. et.al.(1992). Iprodione. Potential tumorigenic and toxic effects in prolonged dietary administration to rats. RNP 346/920808. 15 December 1992.
US, Australia

25. Chambers, P.R. et.al.(1993). Iprodione. Potential tumorigenic effects in prolonged dietary administration to mice. RNP 359/921240. 10 May 1993.
US, Australia

26. Hastings & Huffman (1975/1978 ?). Chronic toxicologic and carcinogenic study with RP 26019 in mice. Toxicology Laboratory. Rhodia Inc. Hess & Clark Division, US. Project CH-42.
Finland, Canada, Australia

27. Hastings (1976). Chronic toxicologic and carcinogenic study with RP 26019 in rats. Toxicology Laboratory. Rhodia Inc. Hess & Clark Division. Project CH-41.
Finland, Canada, Australia

28. Kangas, L. (1991). A 52-week dietary toxicity of iprodione in the beagle dog. Report 84296 from Bio-Research Laboratories Ltd, Canada.
WHO, US, Australia

DEVELOPMENTAL TOXICITY + REPRODUCTION TOXICITY

29. Coquet (1973). Study of the teratogenic activity of the product 26019 RP by oral route in the rabbit. Centre de Recherche et d' Elevage des Oncins. IC-DREB-R 730925.
Finland, US, UK, Australia

30. Coquet (1975/1973 ?). Study of the teratogenic activity of the product 26019 RP by oral route in the OFA rat. Centre de Recherche et d' Elevage des Oncins. IC-DREB-R 731016.
Finland, Australia, UK, US

31. Coquet (1976). Influence of 26019 RP on the reproduction of the rat (3 generation study). Institut Français de Recherches et Essais Biologiques, France. No 760850.
Finland, Canada, Australia, (US ?)

32. Henwood, S.M. (1991). Two-generation reproduction study with iprodione technical in rats: Final report HLA 6224-154. Hazleton Laboratories America.
WHO, US

33. Keets et.al. (1985). A teratology study in rabbits with iprodione. Report WIL-21028 from WIL Research Laboratories, US.
WHO, Finland, US, Canada

34. Tesh, J.M., McAnulty, P.A. & Deans, C.F.(1986). Iprodione (technical grade): Effects of oral administration upon pregnancy in the rat. 1. Dose range finding study. Report 85/RHA063/752 from Life Science Research, England.
WHO, Finland, US

35. Tesh, J.M. et.al.(1986). Iprodione (technical grade): teratology study in the rat. Report 85/RHA064/765 from Life Science Research, England.
WHO, Finland, Canada (marked: Rat definitive study, C.F. Deans), US

METABOLISM IN RAT

36. Hallifax, D.(1989). Iprodione:absorption, distribution, metabolism and excretion study in the rat. Report 89/RPM005/1013 from Life Science Research, England.
WHO, US, Canada

37. Laurent & Buys (1974). Metabolism in the rat.
Finland, Canada, UK, Australia

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WHO

Appendix 2. Table 1

Iprodione: Toxicological Studies

Ref	Study type	End-point	Values/Results					
			WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
	ACUTE TOXICITY							
1.	Acute oral tox	LD_{50}(mg/kg)	3700 (M+F) Wistar-rat					3700 (M/F) Wistar-rat
2.	-"-	LD_{50}(mg/kg)	> 2000 (M) > 2000 (F) purity 97,9% CD-rat	M: Could not be determined F:3629 combined:4468 rat tox category:III - CORE MINIMUM				
3.	-"-	LD_{50}(mg/kg)			4000 (M+F) CD-1 mouse			
4.	-"-	LD_{50}(mg/kg)	> 2000 (M+F) Beagle-dog		> 2000 (M+F) CD-rat	> 2000 (M+F) CD-rat 4000 (M+F) CD-1-mouse > 2000 (M+F) Beagle-dog		> 2000 (M/F) CD-rat 4000 (M/F) CD-1-mouse > 2000 (M/F) Beagle dog
5.	-"-	LD_{50}(mg/kg)	2060 (M) 1530 (F) CD-rat					
6.	-"-	LD_{50}(mg/kg)	1870 (M) 2670 (F) CD-1-mouse					
7.	Acute dermal tox	LD_{50}(mg/kg)	> 30 000 rabbit					> 30 000 rabbit
4.	-"-				rat: no mortality	> 1000 (m+F) NZW-rabbit 2500 (M+F) CD-rat		> 1000 (M/F) NZW-rabbit > 2500 (M/F) CD-rat

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
8.	-"-	LD_{50}	> 2000 (M+F) NZW-rabbit					
9.	Acute inhal. tox	LC_{50}	> 3.29 (M+F) mg/l SD-rat		-not acutely toxic to SD-rat up to dose level of 3.29 mg/l --> could be considered at slightly toxic poison category - particle size analysis not carried out each hour as per EPA/OECD-guidelines -other aerosol producing method should have been used	> 3.29 g/m^3 (M+F) SPF-rat		> 3290 mg/m^3 rat
5.	Acute intraperitioneal tox	LD_{50} (mg/kg)	1330 (M) 700 (F) CD-rat			700 (M) 1330 (F) rat		
6.	-"-		900 (M) 625 (F) CD-1-mouse			900 (M) 625 (F) mouse		
5.	Acute subcutaneous tox	LD_{50} (mg/kg)	> 4500 (M+F) CD-rat			> 4500 (M+F) rat		
6.	-"-		> 6700 (M+F) CD-1-mouse			> 6700 (M+F) mouse		
	IRRITATION							
10.	Dermal irritation	potency	not an irritant rabbit			irr. index 0.00 NZW-rabbit --> non-irritating		not an irritant albino rabbit
11.	-"-		not an irritant rabbit	did not induce irritation tox.category:IV - CORE MINIMUM	average primary irr. score= 0.0 --> non.irritating NZW-rabbit			

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
4.	-"-				no irritant action NZW-rabbit	irr. index 0.00 NZW-rabbit non irritating		not irritating NZW-rabbit
12.	Eye irritation	potency	mild, transient rabbit			washed: not irritant unwashed: mild NZW-rabbit		a slight eye irritant albino rabbit
13.	-"-		-"-	mild tox. cat III - CORE MINIMUM				
4.	-"-				no irritant activity NZW-rabbit	irr. index= 0.00 NZW-rabbit		* not irritating NZW-rabbit
	SENSITIZATION							
15.		potency				* Sulser & Schwartzmethod on guinea-pig * no cutaneous sensitiziting activity		* Dunking Hartley guinea-pigs * not a skin sensitizer
14.	Sensitization	potency	not a dermal sensitizer in guinea-pigs		does not produce any hypersensitivity Büchler-method Hartley-guinea-pig (F)	non-sensitizer Büchler-method Hartley-guinea-pig (F)		

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
	SUBCHRONIC TOXICITY							
17.	Subchronic toxicity 13 weeks in diet/rat	NOEL NOAEL LOEL	Crl: CD(SD)BR-rat * NOAEL= 1000 ppm= (M) 78 mg/kg/d (F) 89 mg/kg/d * ≥ 2000 ppm body weight ↓ + histopatological changes (adrenal glands,uterus, ovaries)					
21.	3 months in diet rat	NOEL NOAEL LOEL	CD/CRJ-rat * NOAEL= 300 ppm = (M) 21 mg/kg/d (F) 24 mg/kg/d * ≥ 1000 ppm microscopic changes in the adrenal cortex * 3000 ppm microscopic findings in the liver, spleen and thymus			CD-rat (Charles River strain) * NOEL= 300 ppm= (M) 20.5 mg/kg/d (F) 23.7 mg/kg/d * 3000 ppm urinary volume and specific gravity ↓ ≥ 1000 ppm swelling of the adrenal glands * 3000 ppm atrophy of hepatic cells with loss of fat and glycogen stock * no effects ophthalmoscopia		

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
18.	5 months in diet/rat (In this study the consumption of the active ingredient was different as 2 weeks than after the 5th week; this was clearly noted only in the Finnish evaluation.)	NOEL NOAEL LOEL			CD-rat; * ≥ 500 ppm body w.gain ↓ food consump. (M+F, non-significant) ↓ * no abnorm. in eyes * NOEL= 150 ppm= 7.5 mg/kg/d * NOAEL= 500 ppm= 50 mg/kg/d due to unpalatability of the diet	CD-rat; * ≥ 500 ppm body weight gain ↓ food consump. (F)↓ * no abnormalities in eyes * NOEL= 150 ppm 14 mg/kg/d during the first two weeks and 7-8 mg/kg/d after the 5th week	rat (strain unspec.) * no treatment related effects * no abnormalities in eyes * NOEL= 1000 ppm ~ 50 mg/kg/d (highest dose)	Charles River CD-rat * no treatment related effects * no abnormalities in eyes * NOEL= 1000 ppm ~ 50 mg/kg/d
16.	weeks in diet/mouse	NOEL NOAEL LOEL	Crl: CD-1(ICR)BR-mouse (260-380 mg/kg/d) * ≥ 1500 ppm enlargement and microscopic changes in the liver and adrenal glands (lowest dose) --> NO NOEL * NOAEL not identified					
20.	3 months in diet/dog	NOEL NOAEL LOEL			beagle-dog; * at top dose 7200 ppm (in gelatine capsules) SGOT, SGPT, AP, LDH ↑, liver, thyroid, spleen and adrenal weight↑; mononuclear infiltrates and Kupffer cell hyperplasia in the liver * NOEL= 2400 ppm = 68 mg/kg/d	beagle-dog; * at top dose 7200 ppm (in gelatine capsules) ALAT, ASAT, AP↑, rel.liver weight↑, slight anaemic tendency hypertrophied liver * ≥ 2400 ppm LDH-act.↑ at 2400 ppm congestion of the mesenteric lymph nodes * NOEL= 800 ppm = 18-22 mg/kg/d	beagle dog; * at top dose 7200 ppm (in gelatine capsules) ALAT, ASAT, AP↑, rel.liver weight↑, blood param.↓ * no abnormalities in eyes * NOEL= 2400 ppm = 60-70 mg/kg/d	beagle dog; * at top dose 7200 ppm (in gelatine capsules) ALAT, ASAT, AP↑, slight liver hypertrophy * no abnormalities in eyes *"haematology examination was unremarkable" * NOEL= 2400 ppm = 60 mg/kg/d

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
22.	21-day dermal rabbit	NOEL NOAEL LOEL		NZW-rabbit * clinical chemistry values stat.sign, but comparable to pre-test values--> not related to treatment * at 1000 mg/kg/d males had some slight effects in the treated skin * LOEL> 1000 mg/kg/d * NOEL= 1000 mg/kg/d * The treated skin area < 10% however the study will not be rejected on this basis since the limit dose was administered over an area~7% of the total surface area. * no stability data --> currently unacceptable core class.: SUPPLEMENTARY * 6 months later the registr. showed that iprodione was STABLE - CORE MINIMUM classification	NZW-rabbit * clinical chem.values stat.sign.,but most of them comparable to pretest values execpt at 1000 mg/kg/d decrease in calcium-values in females, which was stat.different in pretest clin.data * occasional dermal irritation * NOEL= 1000 mg/kg/d * the treated skin area was ~10% of the total body area * a certificate of analysis of each batch included			
19.	3 week dermal study/rabbit	NOEL NOAEL LOEL						NZW-rabbit * at doses up to 500 mg/kg/d (highest dose) did not result in any adverse effects (histopathology conducted only at 500 mg/kg/d)

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
	CHRONIC TOXICITY + CARCINOGENICITY							
23.	52 weeks in diet/dog	NOEL NOAEL LOEL	* beagle dog * at 600+3600 ppm (F) and 3600 ppm (M) slight retinal hyperreflection * at 600+3600 ppm anaemia no changes in the bone marrow, abs. prostate gland weight↓ * at 3600 ppm ALP↑ (plasma), ALT (F, serum)↑, LDH↑ (F), microscopic changes in the liver, adrenal glands and urinary bladder * NOAEL= 100 ppm=4,1 mg/kg/d * Minimal Toxic Effect Level= 600 ppm (24,9-28,3 mg/kg/d) (Heinz bodies explained unclearly)	* beagle-dog * at 600+3600 ppm slight retinal hyperreflection (not a toxicol. effect. However, electron microscopy could have been done), Heinz bodies↑(M), abs.prostate weight↓(M) * at 3600 ppm abs.+rel.liver weight↑, ALP, SGOT, SGPT and LDH↑, abs+rel. adrenal weight↑, rel. prostate weight↓ and in females RBC, PVC, Hb, MCHC↓ and Heinz bodies↑ * LEL= 600 ppm * NOEL= 100 ppm= 4.2 mg/kg/d * May 18, 1987 and Feb 14, 1990 memos:RfD= 0.04 mg/kg/d * CORE MINIMUM	* beagle dog * retinal hyper-reflection↑ with time as well as dose (¬progressive retinal atrophy) * at 600 ppm Heinz bodies↑ (but no erythropoiesis) * at 3600 ppm anaemia effects * at 3600 ppm AP↑, ALT↑ (F, but questionable biological significance), microscopic changes in the liver, adrenals, kidney, gall bladder and urinary bladder * at 600+3600 ppm abs. prostate gland weight↓ * comment: Student's may not be appropriate for most data generated, since it depends on a normal distribution which is difficult to establish with a small sample size (n=5 or 6) * NOEL= 4.2 mg/kg/d			* beagle dog * occasional retinal hyperreflection at 600 and 3600 ppm (judgement:not progressive, of a minor nature and not related to iprodione administ.) * at 3600 ppm changes in haematology parameters+at 600 ppm Heinz bodies↑ * at 3600 ppm AP↑, ALAT (F)↑, bilirubin (F)↑, LDH↑, total protein↑ * at 600+3600 ppm prostate weight↓ * at 3600 ppm histological changes in the liver, adrenal glands, kidneys and urinary bladder * NOEL=100 ppm= 4 mg/kg/d * Threshold level for biological effects= 600 ppm (28,7-31,9 mg/kg/d)

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
28.	52 weeks in diet/dog	NOEL NOAEL LOEL	* beagle dog * the adrenals, kidneys and prostate only weighed * the kidney(F) and prostate(M) only tissues examined * at 600 ppm (highest dose) in females erythrocyte parameters↓ * NOAEL= 400 ppm ~18 mg/kg/d * skin lesions --> common in dogs fed powdered chow	* beagle dog * A bridging data in addition to ref. 23 study above, because a limited number of parameters were investigated * 600 ppm RBC, HGB, HCT↓ = LOEL for systemic toxicity * NOEL= 400 ppm for systemic toxicity (~18 mg/kg/d) * A combined NOEL and LOEL for the two 1-year dog studies are 400 and 600 ppm, respectively. * submitted to the RfD Peer Review Committee (Jun 24,1992) * CORE SUPPLEMENTARY DATA, but the study is acceptable in combination with the previous 1-year dog study (ref.23)				* beagle dog * in females the erythrocyte parameters↓ occasionally, but not dose-related and were comparable with controls at week 52. * NOAEL= 600 ppm= 24,6-26,4 mg/kg/d * scabbing of the skin --> not clear as to whether this was treatment related (no mentioning that not all organs were examined)

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
26.	Chronic and carcinogenic study in mice (1975, 18 months)	NOEL NOAEL LOEL tumors			* albino mice * 1250 ppm(M), rel.adrenal, rel.liver, rel.kidney, rel.heart weight↓ * 1250+500 ppm (F) rel.heart weight↓ * 1250 ppm(F), rel.liver weight↑ and haematuria because of which NOEL= 500 ppm(n. 75 mg/kg/d) * no evidence of tumorigenic or carcinogenic potential	* Carworth CF-1 albino mice <u>-at 12 months:</u> * 1250 ppm(M) rel.adrenals weight↓ * 1250+500 ppm(F) rel.heart weight↓ <u>-at 18 months:</u> * 1250+500 ppm(M) rel.liver weight↓ * 1250 ppm(M) rel. kidney and heart weight↓ * 500 ppm(F) rel.liver weight↑ * NOEL= 200 ppm= 23.3(M)-24.5(F)mg/kg/d * no increase in occurrence of malignant tumors (number of mammary glands and thymus examined were few)		* Carworth CF-1 albino mice * no eye effects * the distribution of the neoplastic and non-neoplastic lesions do not appear to be treatment or dose related -NOEL= 1250 ppm= 171,2(M)-192,7(F) mg/kg/d (No comments on MTD.)

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
25.	Tumorigenicity study in mice (1993, 99/52 weeks)	LEL NOEL tumours		* Crl:CD-1 (ICR) BR mice * 4000 ppm body weight gain↓, benign and malignant liver tumors↑, GPT↑, GOT↑, abs.liver weight↑, liver lesions↑ (also in females at 800 ppm) * 4000 ppm in females benign ovarian tumors (luteoma), luteinization of interstitial cells, corpora lutea absent, prominent granulema cells * 4000+800 ppm vacuolation/hypertrophy of the interstitial cells of testes * LEL= 800 ppm * NOEL= 160 ppm (23(F)/27(M) mg/kg/d) * CORE MINIMUM * "Iprodione has carcinogenic potential"=> Sep.14, 1993 memo: will be presented to the HED carcinogenicity Peer Review Committee				* Crl:CD-1(ICR)BR mice * 4000 ppm body weight↓, ASAT+ALAT↑ * non-neoplastic changes in the liver (hepatocyte enlargement and vacuolation), stomach and testes (hypertrophy of interstitial cells) at 800 and 4000 ppm, and in the spleen, kidneys and ovaries (luteomas) at 4000 ppm * 4000 ppm benign and malignant liver cell tumours↑ * NOEL= 160 ppm= 23(M)-27(F) mg/kg/d

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
27.	Chronic and carcinogenic study in rat (1976, 2 years)	NOEL tumours			* Charles River CD rats * 1000 ppm cholesterol↑ * 1000 ppm rel.adrenals weight↑(F,1 yr), rel.liver weight↑ (M,2 yr) * NOEL= 250 ppm= 12.5 mg/kg/d * Body weights and food consumption were decreased at 1000 ppm due to unpalatability of the diet rather than a toxic effect. * No evidence of tumorigenic or carcinogenic potential	* Charles River CD rats * 1000 ppm rel.adrenals weight↑(F, 1 yr), rel. liver weight↑ (M, 2 yr) * A slight decrease in weight gain in 1000 ppm males. Female treatment groups gained less weight with no dose relationship. * No increase in occurrence of malignant tumors * NOEL=250 ppm= 8.4(M)-10.4(F) mg/kg/d		Unmodified text was obtained from the JMPR (1977) evaluation * 1000 ppm slight reduction in body weight gain * variations in organ weight did not show a group distribution and seemed not to be related to drug administration * No treatment relationship of neoplastic and non-neoplastic findings

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
24.	Tumorigenic and toxic effects in rat (1992; 104/52 weeks)	LOEL NOEL tumours		Crl:CD(SD)BR-rat * 1600 ppm body weight gain↓ food consumption↓, benign testicular tumours↑; which also showed a stat.sign. dose-related trend, atrophy * in prostate * 1600+300 ppm testicular in testitial cell hyperplasia, liver weight↑ and hepatocyte enlargement in males, histopathologic adrenal changes in males, hemosiderosis and haematopoiesis in spleen in females * 150 ppm in males vacuolation of the zona reticularis of the adrenal gland=> in the first evaluation Jun 24, 1993 150 ppm was the LOEL and no NOEL could be set. Thus the study did not ratify the guideline and was only SUPPLEMENTARY. After receiving the historical control data on vacuolation of the zona reticularis, this lesion was considered in the low dose males to be comparable to the mean of the control data * Classification of the chronic tox.segment was upgraded to CORE MINIMUM * Classification of the carcinogenicity segment is to be decided in the review by the HED Cancer Peer Review Committee (Sep 14, 1993 memo)				* Crl: CD(SD)BR-rat * 1600 ppm body weight gain↓, food consumption↓ * no eye effects * at 150, 300 and 1600 ppm rel.adrenal weight↓ in females--> high mean control group adrenal weights--> not treatment related due to the absence of any dose relationship. * 1600+300 ppm hepatocyte enlargement, histopathologic adrenal changes in males, testicular interstitial cell hyperplasia, hemosiderosis in spleen in females * 1600 ppm benign testicular tumors↑ * NOEL=150 ppm= 6(M)8(F) mg/kg/d

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
	REPRODUCTION AND TERATOGENICITY							
34.	Teratogenicity; rat, oral (dose range finding)	NOEL NOAEL	CD-rats ≥ 240 mg/kg/d maternal toxicity; 120 mg/kg/d occasional clinical signs	≥ 400 mg/kg/d marked maternal toxicity 240 mg/kg/d flaccid muscles, 120 mg/kg/d occasionally flaccid muscles		CD-rats ≥ 400 mg/kg/d marked maternal toxic response		
35.	Teratogenicity; rat, oral	NOEL NOAEL	CD-rats Dams: * no adverse effect on maternal health (highest dose was 200 mg/kg/d) * NOAEL= 200 mg/kg/d for maternal tox. Offspring: * 200 mg/kg/d space between body wall and organs slightly↑, a slight effect on fetal development (small in size, not stat.sign.) * NOAEL= 90 mg/kg/d for embryofetal tox. -no evidence of teratogenic potential	SD-derived CD-rats Dams: * NOEL> 200 mg/kg/d for maternal toxicity * Questioning why flaccid muscles were not seen in the definitive study * First this study was core supplementary, but after an answer upgraded to CORE MINIMUM Offspring: * 200 mg/kg/d slightly↓ fetal weights and↑ space between the body wall and organs=LOEL * NOEL= 90 mg/kg/d for developmental toxicity	-SPF-rats Dams: * no maternal toxicity; if the range-finding study were taken into consideration-> a definitive NOEL for maternal tox. 90 mg/kg/d Offspring: * 200 mg/kg/d slight viscoral immaturity= space between body wall and the organs↑. This was regarded as a non-specific effect of relatively little importance. * NOEL=90 mg/kg/d for fetotoxicity * NOEL= 200 mg/kg/d for teratogenicity (no indications of teratogenic activity)	* CD-rats; by gastric intubation Dams: * no effects Offspring: * 200 mg/kg/d space between body wall and organs↑ -> indicative of slight immarity, small fetuses * NOEL=90 mg/kg/d for embryotoxicity		

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
30.	Teratogenicity; rat, oral			-OFA(SD)-rats Dams: * 400 mg/kg food consumption↓, slight↓ body weight gain * NOEL= 200 mg/kg for maternal tox. Offspring: * 400 mg/kg number of implantation sites↓ * "Since it is highly unlikely that no abnormalities (except chequered sternum) were noted the registrant is requested to submit the historical data for this strain and raw data for this study" * NOEL= 200 mg/kg for fetal toxicity * NOEL> 400 mg/kg for teratogenic effects * CORE MINIMUM DATA		-OFA(SD)-rats Dams: * maternal toxicity at all dose levels (≥ 100 mg/kg/d); weight gain↓ Offspring: * 400 mg/kg/d sites of implantation↓ * NOEL= 400 mg/kg/d for teratogenicity	SD-rats Dams: * a dose related decrease in bodyweight gain-> NOEL for maternal tox. is not established Offspring: * 400 mg/kg number of implantations↓ * In all treatment groups mean fetal weight slightly↓ * no malformations or treatment related variations * no evidence of fetotoxicity or teratogenocity	-OFA(SD)-rats Dams: * 400 mg/kg/d slight decrease in body weight and food consumption * NOEL=200 mg/kg/d for maternotoxicity Offspring: * no treatment related embryotox. or developmental effects * NOEL=400 mg/kg/d for developmental tox.

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
33.	Teratogenocity; rabbit, oral	NOAEL NOEL	* NZW-rabbits Dams: * 200 mg/kg/d weight, food consumption↓ * 60 mg/kg/d slight body weight loss => NOAEL= 20 mg/kg/d for maternal tox. * 200 mg/kg/d is an excessive dose for teratology evaluation Offspring: * 7/18 females receiving 200 mg/kg/d aborted, and 2/10 had totally resorbed litters resulting only 8 viable litters at the high dose * NOAEL= 60 mg/kg/d for embryofetal tox.	* NZW-rabbits Dams: * 200 mg//kg/d weight and food consumption↓ 60 mg/kg/d body weight gain↓ (p< 0.05) NOEL= 20 mg/kg/d for maternal tox. Offspring: * 200 mg/kg/d 7/18 females aborted, 2/10 a total resorption-> 8 high dose litters are too few to make stat. analysis meaningful * 20 and 60 mg/kg/d umbilical herning↑ (not stat.sign.) * 200 mg/kg/d skeletal variations↑ and were apparently related to delayed ossification * NOEL=60 mg/kg/d for developmental toxicity * CORE MINIMUM	* NZW-rabbits * 200 mg/kg/d weight, food consumption↓ * 60 mg/kg/d weight loss both initially and in the final days of the study * NOEL=20 mg/kg/d for maternal tox. Offspring: * 200 mg/kg/d 7 abortions=> attributed to maternal tox. * umbilical hernia↑ (not stat. sign) at 20 and 60 mg/kg/d, but not at 200 mg/kg/d * But at 200 mg/kg/d aborted fetuses were not included in any tabulation or stat. analysis=> "it may be prudent to consider 20 mg/kg/d as a NOEL with respect to umbilical hernia" = "a conservative NOEL for teratogenicity" * NOEL= 60 mg/kg/d for fetotoxocity	* NZW-rabbits Dams: * 200 mg/kg/d weight, food intake↓ * 60 mg/kg/d slight body weight loss * NOEL= 20 mg/kg/d for maternal tox. * 200 mg/kg/d was maternally too toxic for a complete teratologic evaluation Offspring: * 7/18 females aborted at 200 mg/kg/d=> a secondary effect of maternal toxicity * 200 mg/kg/d a slight increase in post-implantation loss (2 females with total litter resorption) * NOEL = 60 mg/kg/d for embryo/fetotoxicity and teratogenicity		

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
29.	Teratogenicity; rabbit, oral	NOEL		* NZW-rabbit Dams: * 400 mg/kg/d 9/17 died * 200 mg/kg/d food consump.↓ * body weight gain↓ in all treated groups * NOEL for maternal tox. could not be demonstrated Offspring: * a dose-dependent↑ in the % of resorptions, ↓ in fetal birth weight and mean live fetuses per litter * a dose-dependent↑ in ossification retardation with sign. diff. even at the lowest dose (absence of one or more sternebrae); which can provide valuable supportive evidence of fetotoxicity => NOEL for fetal toxicity could not be determined, study considered only as CORE SUPPLEMENTARY since dosing did not encompass the entire period of major organogenesis (was: days 6-16 should be: days 6-18)		* NZW-rabbit Dams: * 400 mg/kg/d 9/17 died * 200 mg/kg/d food consumption↓, a slight↓ in weight gain * NOEL= 200 mg/kg/d for maternal tox. Offspring: * 400+200 mg/kg/d total resorptions * 4 of the 6 foetuses obtained at 400 mg/kg/d had one rib missing * NOEL= 100 mg/kg/d for embryotox. * there were no signs of teratogenicity	* NZW-rabbit Dams: * 400 mg/kg 9/17 died * 200 mg/kg body weight↓, a slight food consump.↓ * 100 mg/kg body weight gain↓ * NOEL=100 mg/kg for maternal tox. Offspring: * 400+200 mg/kg early and late resorptions * 3/6 foetuses at 400 mg/kg had a missing rib * NOEL= 100 mg/kg for fetotoxicity * No evidence of teratogenicity	* NZW-rabbit Dams: * 400 mg/kg/d 9/17 died * 200 mg/kg/d slight↓ in body weight and food consumption * 100 mg/kg/d body weight gain↓ => NOEL for maternotoxicity was not demonstrated Offspring: * 200 mg/kg/d total resorption in 23% of females * NOEL= 100 mg/kg/d for embryotox. * No teratogenicity was observed

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
32.	2-generation reproduction	NOAEL NOEL LOEL	* Crl:CD BR/VAF/Plus-rats Adults: * > 1000 ppm body weight↓, body weight gain↓, food consumption↓ * NOAEL= 300 ppm≈ 21 mg/kg/d for parental tox. Offspring: * 2000/3000 ppm during lactation unkempt or hunched appearance, slow, movement, tremors, litter size of live pups↓, pup weight↓ * NOAEL= 1000 ppm for embryofetal tox.	* Crl:CD BR/VAF/Plus-rats Adults: -> 1000 ppm body weight↓, body weight gain↓, food consumption↓ * LOEL=1000 ppm= 69 mg/kg/d * NOEL=300 ppm for parental tox. ≈21 mg/kg/d Offspring: * 2000/3000 ppm during lactation reduced mobility, unkempt appearance, hunching, tremors, viability↓, body weight↓ * LOEL=2000 ppm= 178 mg/kg/d * NOEL=1000ppm= 69 mg/kg/d for reproductive toxicity * CORE MINIMUM DATA (-Deficiency:Food efficiency was not reported)				

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
31.	3-generation reproduction first 5 weeks: 0, 125, 250 and 1000 ppm thereafter: 0, 250, 500 and 2000 ppm	NOEL		Found in the memorandum of ref.32 that this study is accepted, but it is not mentioned in the bibliography and no DER was available	* SD-rats * NOEL=250 ppm (12.5 mg/kg/d) for reproductive tox., based on the decreased litter size and post natal growth at 1000 ppm of the F_1 gen. * NOEL=125 ppm (6.25 mg/kg/d) for general toxicity, based on the decreased body weights in the pups during weaning and decreased kidney weight.	* SD-rats * at 2000 ppm the postnatal pup growth↓ in reproduction of F_0-F_1 * NOEL=500 ppm= 28.7 mg/kg/d		* OFA(SD)-rats * 2000 ppm a slight but stat.sign. decreased litter size * 2000 ppm a slight but NOT stat.sign. reduced pup body weight * NOEL= 500 ppm =30 mg/kg/

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
	METABOLISM IN RAT							
36.	Absorption, distribution, metabolism and excretion in the rat (oral single and multiple doses)	extent of abs., distr., biotrans. and elimin.	* Charles River CD-rat After single low dose * EXCRETION: in urine 67%(M), 53%(F) and in faeces 25%(M), 39%(F) * peak blood conc. 2-4 h * 7 d:< 0.3% in tissues * elimin. t1/2= 9h(M)/7h(F) After single high dose * EXCRETION: in urine 43%(M), 46 %(F) and in faeces 56 %(M), 52 %(F) * peak blood conc. 6 h * 7 d:< 0.2 % in tissues * elimin. t1/2= 20 h(M), 13 h(F) After multiple low dose * EXCRETION: in urine 75%(M), 65%(F) and in faeces 20%(M), 28%(F) * tissue conc. < 1 ppm * The excretion was rapid. * The absorption was poorer with a high dose than with a low dose	* Charles River CD-rat * Readily absorbed, metabolized and excreted; abs. and elimin. from the blood fit a one-compartment model * peak blood conc.= 2h(F)/4h(M) low dose and 6h high dose * elimin. t1/2= 6.9h(F)/8.9h(M) low dose, 12.5h(F)/19.8h(M) high dose * Distribution: widespread but the levels were low, bioaccumulation is not extensive * ELIMINATION: in low and repeated dose rats primarily in urine (53-75%) and in high dose rats primarily in feces (52-56%) => Absorption and metabolism of the high dose is near saturation * A metabolic scheme * Since HPLC and TLC failed to identify at least 2 major urinary metabolites and up to 22% of the urinary radioact. and up to 88% of the fecal	* rat * Rapid absorption, extensive distribution (but low) and metabolism * peak blood conc.= 2h(F) 4h(M) low dose and 6h high dose * elimin. t1/2= 6.9h(F)/8.9h(M) low dose, 12.5h(F)/19.8h(M) high dose * ELIMINATION: after low single or multiple dose mostly via urine (53-75%) and after single high dose about the same amount in faeces and urine * In faeces 30%(low dose) or 80%(high dose) was unmetabolised iprodione. * A metabolic scheme * 21% remains in the body after 7d			

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
36. cont'd			* A metabolic scheme; females eliminated more as a parent compound in urine	radioact.=> classification: UNACCEPTABLE as a metabolism study				
37.	Metabolism in the rat (single dose, non labelled)	% in excreta			* Charles River COBS rat * Elimination is very rapid RESIDUES: in faeces: 53% iprodione, 2,3% metab. with unhydr. benzene ring, 3,5% metab. with hydr. benzene ring in urine: 3% iprodione, 11% RP 32490 and RP 25040, 0,5% RP 30228, 4% metab. with unhydr. benzene ring, 7,8% metab. with hydr. benzene ring in tissues: none	Ref 37+38 combined: * very rapid abs. and elimin. * 2/3 in urine and 1/3 in faeces * Large number of metab. detected; the main products are 16% iprodione, 20% RP 32490 and 8% RP 36114 * A metabolism scheme	* rat * ~100% of the dose excreted within 72h (72% in feces/25% in urine) * In feces: 53% iprodione, 2.3% metab. with non-hydr. benzene ring, 3.9% metab. with hydr. benzene ring * In urine: 3% iprodione, 11% metab. 2 and 3, 0.5% metab. 1, 4% metab. with non-hydr. benzene ring, 7.8% metab. with hydr. benzene ring	* rat * Excretion is rapid * 86% of the ingested dose in urine 26% and in faeces 59% * unchanged iprodione in urine 3% and in faeces 53% * A metabolism scheme
38.	Metabolism in the rat (single dose, labelled)	% in excreta			* Charles River rat * Excretion was rapid; 62% in urine, 36% in faeces, < 0.005% in exhaled air * In faeces: iprodione + 6-7 metab. of 1-2.2% and 20 metab. of < 1% * In urine: iprodione + 2 major metab. and 20 metab. together of 10.5%		* rat * In 96h 62% excreted in urine and 36% in feaces * 13 metab. were identified * 10 metab. unidentified * In urine main metab. were 2 and 5 * A metabolism scheme	* rat * Elimination complete in 96h; 62% in urine and 36% in faeces (exhaled air negligible) * a large number of metab. was detected; 10% iprodione in faeces and 5-6% in urine * A metabolism scheme

Ref.	Study type	End-point	WHO/JMPR	US	CANADA	FINLAND	UK	AUSTRALIA
39.	Percutaneous metabolism in the rat (labelled)		* Hairless strain rat * dermally abs. 0.65% in 24h, of which 0.45% in excreta and 0.15% in carcass * In faeces: iprodione, RP 36114 * In urine: iprodione, RP 36114, RP 32490 and RP 30228 in males					
	CONSIDERATION OF THE LOWEST NOEL AND THE POSSIBLE ADI-VALUE IN THE EVALUATIONS		1977: ADI= 0-0.3 mg/kg/d, 1992 review evaluates studies made available since 1977 1992: ADI= 0-0.2 mg/kg/d based on several studies NOAELS: mouse: 600 ppm= 115 mg/kg/d (4 weeks) rat: 300 ppm= 21 mg/kg/d (2-gener.) rabbit: 20 mg/kg/d (teratolog.) dog: 400 ppm= 18 mg/kg/d (second 1-year study)	Registration Eligibility Document (RED) is not yet available, since many acceptable studies are missing for re-registration * RfD has been 0.04 mg/kg/d based on the NOEL= 100 ppm from the 1 year dog study (ref.23). However, RfD may be raised because of the new NOEL of 400 ppm (18 mg/kg/d, ref. 28)	Not mentioned	NOEL= 7 mg/kg/d (5 month rat study) ADI= 0.07mg/b.w./d (Notice that the 1 year dog studies were not submitted to FIN. The 5 month rat study was submitted to CAN, UK and AUS, but they reached a higher NOAEL in that study)	ADI=0.3 mg/kgb.w./d agreed with WHO (1977) => The theoretical max. intake of iprodione from lettuce is well within ADI. (Max. number of treatments:3 per crop and latest time of appl: 4 weeks before harvest)	* NOEL=4 mg/kg/d (1 year dog study ref. 23) * ADI= 0.04 mg/kg/d

Appendix 3

AUSTRALIA

Descriptive Terms for Acute Toxicity

Oral	**LD_{50} (mg/kg)**
extreme	< 10
high	10 - 50
moderate	50 - 500
low	500 - 5,000
very low	> 5,000

Dermal	**LD_{50} (mg/kg)**
extreme	< 50
high	50 - 200
moderate	200 - 2,000
low	2,000 - 20,000
very low	> 20,000

Inhalation	**LC_{50} (mg/m^3)**
high	< 200
moderate	200 - 2,000
low	2,000 - 20,000
very low	> 20,000

Eye irritation	
corrosive	
severe	irreversible corneal opacity
moderate	reversible corneal opacity
slight	no corneal opacity, transitory irritation
none	nil

Skin irritation	
corrosive	
severe	severe irritation at 72 hours
moderate	moderate irritation at 72 hours
slight	slight irritation at 72 hours
none	nil

Skin sensitization	
high	strong response in all animals
moderate	response in all animals
weak	response in some animals
none	nil

NH & MRC / Drugs and poisons schedule committee
First aid and safety directions sub-committee

Classification Criteria for Safety Directions

Oral toxicity (LD_{50})		
Extreme	less than 10 mg/kg	100 130 133
High	10-50 mg/kg	100 130 133
Moderate	50-500 mg/kg	130 133
Low	500-5,000 mg/kg	129 133
Very low	> 5,000 mg/kg	Nil

Dermal toxicity (LD_{50})		
Extreme	less than 50 mg/kg	100 131 290 292 294 296 291? 298? 330-342
High	less than 200 mg/kg	100 131 290 292 294 296 330-342
Moderate	200-2,000 mg/kg	130 131 (129 131?) 290 294 (292?)
Low	2,000-20,000 mg/kg	Nil
Very low	> 20,000 mg/kg	Nil

Inhalation toxicity (LC_{50})		
High	less than 200 mg/m^3	100 132 300 (301?) (canister 302?) 310?
Moderate	200-2,000 mg/m^3	130 132 (300?) (303?) (306?) (315?)
Low	2,000-20,000 mg/m^3	219 (221) (222) (223) (if equipt indicated)
Very low	> 20,000 mg/m^3	Nil

Extras

163	Nose and throat. Only if data indicates
220 (221) (222) (223)	To be used if equipment is indicated
219 (avoid inhaling)	To be used if no equipment is specified for LOW hazard
315	Disposable respirator
219	Avoid inhaling

Eye irritation		
Corrosive	205 206 162 290 297	Also use first aid statement "s"
Severe	206 162 290 297 340 343	Corneal opacity, not reversible 7/7
Moderate	161 162 290 299 340 343	Corneal opacity, reversible 7/7
Slight	160 162 (TGAC) 210 211 161 162 (EUP) 210 211	No corneal opacity
None	Nil	No irritation

Note:
- First aid statement "s" is only specified for corrosive chemicals because of the difficulty of getting people to wash eyes for 15 minutes with non-isotonic water.
- 343 would be suitable for "severe" and "moderate".
- NB: If equipment is specified do not use 210 and 211.

Skin irritation		
Corrosive	205 206 164 290 292 293 294 298 330-342	
Severe	206 164 290 292 294 296 330-342	Severe irritation at 72 hours
Moderate	161 164 290 292 294	Moderate irritation at 72 hours
Slight	160 162 (TGAC) 161 164 210 211 290 294 (312?) (EUP)	Slight irritation at 72 hours
None	Nil	No irritation

Waterproof clothing is reserved for the really severe skin irritants.

Skin sensitization		
Moderate and High	180 181	No equipment is specified as no amount of safety equipment will protect an operator from exposure and reaction. A low grade (moderate) dermatitis within a few days can be a flaring erythema (high) in humans. Skin sensitizations are absolute hazards once they are established.

Aerial application safety directions
These are not addressed by the SUSDP as the civil aviation instructional manual which is the basis for registration of crop-spraying pilots requires the pilot to employ proper occupational health procedures when preparing and loading pesticides. Mixers (who handle the concentrate) are the most vulnerable; the loaders not so much (use of closed systems); markers are also vulnerable.

Other Appendix H statement		
280	Opening the container	To be used when there are really severe eye problems from a liquid concentrate or toxic dust
283	Using the product	To be used for dusts or undiluted ULV
140	Do not touch or rub the eyes, nose or mouth with hands	To be used for granules in conjunction with 141 (when handling granules)
190	Repeated minor exposure may have a cumulative poisoning effect	To be used routinely on anticholinesterase chemicals and for other chemicals on their merits
251	Do not touch the bait. Use scoop or measure	To be used routinely for loose bait
252	If on skin and after each baiting, wash thoroughly with soap and water	To be used routinely for loose bait
309	Detailed instructions for safe use appear in State regulations	This is used for fumigants
310	If dust is present	This is used for dusty granules
370	Do not re-use footwear unless thoroughly aired	This is to be used for volatile pesticides

Home garden	
292 (a)	Cotton overalls buttoned to the neck and wrist (or equivalent clothing) and washable hat
312	Rubber gloves
296	Face shield
300 or 314	Half-face respirator or disposable respirator (SAA 1716)

- Toxicological data on EUP is mandatory
- Minimum pack size
- Uniform maximum concentration for each chemical

New terms			
205	Corrosive	206	Attacks
219	Avoid inhaling	314	Disposable respirator

Amended 3 JAN 91

PART 2: ENVIRONMENTAL FATE AND ECOTOXICOLOGY

2.1 Introduction

The countries participating in the environmental fate and ecotoxicology part of the Iprodione Phase 3 were:

- Sweden (evaluation 1991)
- The Netherlands (evaluation adopted 1988, supplemented 1989)
- The United States (separate reviews 1981-1992)
- Finland (evaluation 1991).

Iprodione Phase 3 Report concerns the following study areas evaluated by the participating countries as follows:

Fate and behaviour of iprodione in the environment

- Hydrolysis:
  Finland, Sweden, the Netherlands, the US

- Photodegradation in water:
  Finland, Sweden, the US

- Soil metabolism, aerobic and anaerobic in representative soil types:
  Finland, Sweden, the Netherlands

- Biodegradation in aquatic systems, aerobic and anaerobic, including identification of breakdown products and metabolites:
  Finland, Sweden, the Netherlands, the US

- Mobility/leaching in representative soil types and mobility of metabolites and breakdown products:
  Finland, Sweden, the Netherlands

- Adsorption/desorption in representative soil types including metabolites and breakdown products:
  Finland, Sweden

Ecotoxicity of iprodione

- Avian acute oral LD_{50}:
  Finland, Sweden, the Netherlands

- Avian dietary toxicity LC_{50} - terrestrial and aquatic bird:
  Finland, Sweden, the Netherlands

- Fish acute toxicity LC_{50} freshwater warm- and cold water species:
  Finland, Sweden, the Netherlands

- Daphnia immobilization test:
  Finland, Sweden, the Netherlands

- Alga, growth inhibition:
  Finland, Sweden, the Netherlands

- Acute toxicity to honey bees LD_{50}:
  Finland, Sweden, the Netherlands

- Earthworm, acute toxicity test:
  Finland, Sweden

Field studies have not been taken into account in this Iprodione Phase 3 Report. Instead, studies conducted with products or a few studies made with breakdown products have been evaluated.

The study areas considered by participating countries are presented in the references I (Appendix 1).

2.2 Types of data reviews

2.2.1 Language

The review of Sweden was only available in Swedish except for the summary. The Finnish evaluation was translated into English. In the Dutch review the studies were reported in English, but the conclusions were written in Dutch and later translated into English.

2.2.2 General description of the reviews

Sweden and Finland

The Swedish and Finnish reviews were generally quite similar. They were written according to the Nordic guidelines for evaluating pesticides. The Swedish review (105 pages including one appendix), however, was written in much more detail. In the Finnish review (31 pages, including appendices), only the most important background information (pH, ^{o}C, soil properties etc.) and the performance of the study were described, but not for example analysis methods.

In the Swedish review, each study was reported in three parts as follows: the first part covered **the performance of the study** containing information on conditions, test and analysis methods etc. The second part discussed **the results** and quite often tables were used to present results of the fate and behaviour studies, especially. Finally there were **the comments** of the reviewer, for example, as to whether the study was conducted according

to a test guideline, whether there were some deficiencies, etc. It is very useful to have comments immediately after the study. The report also noted which studies were not taken into account in the conclusions, and the reasons for rejecting them.

Both the Swedish and the Finnish reviews contained separate summaries about fate (or "exposure" as written in the Swedish review) and effects of the iprodione. Finally a hazard assessment was made and in that chapter results concerning fate as well as the effects of iprodione were considered together. Additionally at the beginning of the Nordic reviews a short written summary was presented and also a numerical summary with mainly endpoint values. Also the degradation pathways and products were shown in the appendices.

The Netherlands

The Dutch way of evaluating (review containing 27 pages) the fate and effects of iprodione was rather similar to the Finnish and Swedish assessment. First, study by study, a short numerical summary was presented on important background information and results. Additionally the performance of the study and results were presented. The studies were considered in more detail than in the Finnish review. The way the tables were used to show the results was clear and helpful. Comments or remarks on every study, if needed, were also given, although very briefly (Comment, J.B.H.J. Linders 22.4.1994: nowadays the Dutch reviews contain more detailed remarks and explanations of whether the study was useful or not for evaluation purposes). Also the degradation pathways and products were shown as in the Finnish and Swedish reviews.

The main difference between the Dutch and the Nordic reviews was the way the conclusions were made. In the Dutch review, the previously presented numerical results were summarized, generalized and presented one more time mainly as values in the conclusions. Model calculations were used to predict concentrations in the environment. DT_{50} -value used for the calculation of leaching and accumulation was stated as 41 days and K_{om} -value 281 dm^3/kg. Based on the model calculation, "Steungroep-M", the following information was obtained: a concentration in the upper ground water (< 0.001 mg/m^3); leaching from the top 1 m soil layer (< 0.001% of the dose); a concentration remaining after 1 year (20 µg/kg). Similarly a concentration in aquatic systems was predicted (dosage level 0.25-2.0 kg/ha may lead to concentration 2-80 µg/l in a ditch with a depth 25 cm and treatment emission of 2-10%) and a risk assessment made by comparing that result with the toxicity of iprodione to water organisms. Concentrations in the environment predicted with models were not presented in the Nordic reviews.

The United States

The American way of pesticides evaluation was quite different from the other participating countries. A separate scientific report **(Data Evaluation Record)** was written on each study. The reports were very detailed and, for example the analysis methods used were described. In the reports, **the materials and methods** were presented first and then **the results**. Tables were used to show the results. The **discussion part** gave a very accurate presentation of the deficiencies of the study. Their own calculated values were given as endpoints instead of the results given by the authors. On the basis of individual Data

Evaluation Records a **Memorandum** is prepared and finally, when all adequate studies have been received, a **Re-registration Eligibility Document** (RED) is written. This document contains summaries of the toxicological, ecotoxicological and environmental fate studies and also a risk assessment and administrative measures. Because a RED concerning iprodione has not been yet prepared, there is as yet no summary , hazard or risk assessment available on iprodione.

It should be kept in mind that the status of the available reviews is quite different. All that was available from the US was individual, scientific study reports. These reports did not consist any conclusions, hazard or risk assessment. The reviews made by Finland and Sweden also considered hazards of iprodione. Finland gives the final environmental risk assessment in a statement written by the National Board of Waters and the Environment. In Sweden an administrative document considering toxicological and ecotoxicological risks, benefits and analysis of consequences is made partially on the basis of an environmental review. The Netherlands decides the approval of a pesticide on the basis of available review.

2.2.3 Reference lists

The styles for citing references seemed to be different in the available reviews: some countries listed studies according to the authors' names, others according to the laboratories. In some cases it was difficult to decide whether the participating countries had evaluated the same study. For example Finland, Sweden and the Netherlands presented the same results concerning soil degradation, but the study reports were cited differently (Ref. 8a., 8b. and 8c.). Sweden and the Netherlands presented the results in a more detailed fashion but obviously the countries reviewed the same study, although it is possible that they had different versions of the study report.

2.2.4 Test guidelines, GLP

Only Sweden provided information on whether the studies followed certain, well-known test guidelines. Sweden also reported deviations from the test guidelines. Finland only mentioned in the conclusions that some of the latest studies had been made in accordance with OECD guidelines.

The importance of GLP was not emphasized in the reviews at all.

2.2.5 Quality of the data

Finland gave a brief statement on the quality of the data available, and specified studies that were lacking. Sweden mentioned only that further information was needed on the effects of the degradation product, RP 30228, but did not specify the studies which should be required. The Netherlands emphasized the lack of information concerning leaching and accumulation of RP 30228.

The US had a useful way of showing in a summary table whether additional data was required. That table also listed the studies which had been accepted.

2.2.6 Rejection of the data

Sweden stated, in a sort of introduction before the presentation of each study area, how many studies were available and which of them had been accepted. Some of the studies were only mentioned in the references; others were presented and detailed reasons given for the rejection. It was clear which studies had been taken into account in the reviewer's conclusions.

The US also showed clearly whether or not each study was acceptable and what kind of studies were still required.

In the Dutch review no rejection of the studies was mentioned in the text, but according to the reference list all the studies available were not accepted. The references were classified on the quality and relevance of the delivered data as follows:

1. Reference is included in the summary
2. Reference is included in the summary, except in RIVM (= National Institute of Public Health and Environmental Protection) conclusion. Only when the concerning studies of category (1) are lacking, this study is also mentioned in RIVM conclusion, with a remark on the value of the delivered data.
3. Reference is not included in the summary except when no data are available in the categories 1 and 2.

It would be more informative to state the acceptability of a study in the text and not only in the reference list.

Finland criticized some studies, but all the data had obviously been taken into account in the conclusions.

The Swedish review mentioned that Swedish authorities do not rely on, or even evaluate studies conducted by Industrial Bio-Test Laboratories Inc (IBT) (Ref. 24). The Dutch authorities also usually consider IBT studies unreliable. Evaluating IBT's study (Ref. 24) was a mistake, according to the Dutch comments (J.B.H.J. Linders 22.4.1994).

2.3 Comparison of values/results reported in the data reviews

The results of the comparison of the reviews are presented in tables 1 (Fate and behaviour in the environment; see Appendix 3) and 2 (Ecotoxicity, see Appendix 4). References are arranged according to the study area (References I; see Appendix 1) and also shown in alphabetical order (References II; see Appendix 2).

Hydrolysis

There were three different hydrolysis studies: study 1 was available in Finland, Sweden and the Netherlands (Sweden had also an additional report to study 1 (Ref. 2)); study 3 in Sweden and the Netherlands; and study 4 only in the US.

Finland stated the results of study 1 briefly. Sweden and the Netherlands analysed the hydrolysis and presented, in addition to the DT_{50}-values, the degradation products and their amounts at different pH-values and at different iprodione concentrations used. Actually the results given were the same in all the countries. Sweden criticized the study because there was no indication of whether the study had been carried out under sterilized conditions. The Netherlands accepted the study (classified as category 1 according to the references).

The Swedish review found more deficiencies in study 3 than it had in study 1. Both Sweden and Finland reported the same DT_{50}-values, but Sweden had also calculated their own DT_{50}-values. Sweden stated that it was possible to accept the study because the results of the available hydrolysis studies (Ref. 1, 2 and 3) supported each other.

The US presented study 4 in quite some detail, for example the amounts of the degradates were reported at different times. The DT_{50}-values given by the study authors were criticized and had not been accepted. The study was accepted however, but the presented DT_{50} -value was calculated using a model. The calculated value was much higher than those in the other countries' reports.

Photodegradation

Sweden had two photodegradation studies in water. Study 6 was mentioned only in the references, but not reported because iprodione was exposed to wave lengths not corresponding to natural light. Both Finland and Sweden had study 5, but Sweden reported two parts of the study. The given endpoints were the same. Sweden stated that iprodione photodegrades, but it was impossible to evaluate photodegradation under natural conditions, because there were uncertainties in the report (the study was poorly reported; it was not clear whether the conditions corresponded to natural conditions, etc.). Sweden did not take the results into account in the conclusions.

The US had not accepted the available photodegradation study (Ref. 7). For example the number of duplicates, sampling intervals and identification of the degradates were unclear.

Degradation in soil

The participating countries had three different studies dealing with degradation in soil (Ref. 8-10). Sweden presented the studies in a very detailed manner. The reviews of Sweden and the Netherlands contained quite a lot of tables which were helpful in understanding the idea of degradation. The Finnish report was not as detailed and it failed to mention whether the study had not been accepted.

One of the studies (Ref. 8a, 8b, 8c) is assumed to be available in Finland, Sweden and the Netherlands although the study reports have different names. It is also possible that the study report available in Finland was not as detailed as those used in Sweden and the Netherlands.

Sweden has not accepted one study (Ref. 9b) because of the contamination of the sterilized controls. The results are presented in the review, but have not been taken into account in the final conclusions. Obviously Finland had the same study but it had different

title (Ref. 9a). Finland did not criticize the study. The results reported were the same in both reviews.

The countries have all presented the same half-lives for iprodione. Also the results dealing with the metabolites are roughly similar although more details were given in the Swedish and Dutch reviews. Sweden and the Netherlands have also assessed a half-life for the metabolite RP 30228; Sweden > 300 days (Ref 10) and the Netherlands 130 days (Ref. 8 c). In the Dutch review DT_{50} -value (41 days) used in the model calculations has been stated on the basis of one study (Ref. 10).

The final conclusions are quite similar in the Swedish and Finnish reviews. The main discovered points are the following: iprodione degrades in soil to RP 30228, which actually is not a degradation product but rather a structure isomer; RP 30 228 degrades more slowly than the active ingredient; cold conditions slow the degradation and probably iprodione is still found in soil in the next growth season. The Swedish review pointed out that the half-lives of iprodione given by the authors are only the first half-lives. For instance, the first half-life of iprodione in clay loam is 50-70 days, the second 2-3 months and the third 4-6 months. Also Finland commented that the real half-lives of iprodione are longer because the first degradate is not a real degradation product but a structure isomer. Sweden also stressed the importance of pH and bound residues in soil metabolism.

The review of the Netherlands did not contain a written hazard assessment similar to what was done by Sweden and Finland. However, the final numerical conclusions were the same.

Biodegradation in aquatic systems

The participating countries had four different studies (Ref. 11-14) dealing with biodegradation in aquatic systems. Sweden, the Netherlands and the US described the conduct of the study, the experimental conditions and analytical methods in adequate detail. Finland's presentation was relatively short and general.

All the countries had two of the referred studies (Ref. 11 and 12). Finland reported only the recovered fractions of original radioactivity as the endpoint of study 11. The others gave a DT_{50} -value of 2.9 days. Finland and the Netherlands accepted the study. The Netherlands classified the study as "category 2", but the study was accepted because of the lack of "category 1" studies.

The US specified the rejection reasons clearly: all degradation products were not characterized, the material balance was incomplete and variable, and no soil was in the study. Sweden mentioned different reasons: degradation of iprodione occurred possibly via hydrolysis because of pH (6.7) and the microbiological activity was not controlled.

Also study 12 was rejected by the US because of a number of deficiencies: the sediment was misclassified; the study was conducted over too a short time. In the review their own DT_{50} -value, 13.7 days, calculated by linear regression analysis was given. The others presented a DT_{50} -value of 6.4 days in water and 126 days in the whole system.

Sweden had used the review of the Netherlands to support their own documentation. Study 14, considering degradation of RP 30228, was not available in Sweden but it has been referred on the basis of report of the Netherlands.

The reviews of Finland and Sweden contained some kind of hazard assessment. But it must be said that little of the results previously presented were considered.

Adsorption

Finland and Sweden had the same adsorption study available (Ref. 15). Results were shown as K_{oc} -value and both gave almost the same the endpoint (perhaps there is a slight typing error in one or the other value). However, they came to the same conclusion: iprodione is slightly mobile. Desorption values were also reported.

Mobility and leaching

Sweden and Finland shared one mobility study (Ref. 16). That bioassay study was not conducted according to the recognized test guidelines. Both Sweden and Finland reported the same results, but Sweden did not take the study into account in the conclusions.

Sweden and the Netherlands had a two-part soil column leaching study (Ref. 17). The same results were given and the conclusions contained a summary that iprodione and its degradates were no more than slightly mobile. Sweden stressed that iprodione was more mobile in silty clay loam. Rf(column) -values calculated with data given by the author were presented in the Dutch review, which also showed Rf(column)-values and converted K_{om}-values used for the RIVM conclusion. Those values have been referenced to in the Swedish review.

Avian toxicity

There were two acute oral avian tests available in Sweden, Finland and the Netherlands (Ref. 18,19). The given endpoints were exactly the same in the first study (Ref. 18). In the other study (Ref. 19) there was no mortality in the highest concentration and Finland and the Netherlands stated a LD_{50} -value of > 10 400 mg/kg, while Sweden gave none.

Four different subacute studies (Ref. 20-23) were available, but one of them (Ref. 20) was only available in Sweden, Finland and the Netherlands. All the countries stated that iprodione was slightly or moderately toxic to birds upon acute oral exposure. However, Sweden's conclusions emphasized that iprodione poses a potential risk of to birds if iprodione-containing products such as seed dressings are used and the seeds are not planted deep enough in soil.

Aquatic toxicity

Sweden and Finland had five acute fish toxicity tests (Ref. 24-28) in common. Study 24 was also available in the Netherlands but studies conducted in IBT-laboratories are not usually accepted in the Netherlands (Comment J.B.H.J. Linders 22.4.1994). The US also had study 27. Sweden did not present the results of study 24 at all and did not accept it, because of the laboratory,s unreliability (see § 2.2.6).

The results of the acute fish toxicity tests were the same except that Finland did not present any NOEC-values except for one study.

The participating countries had four tests available of acute toxicity to Daphnia (Ref. 29-32). Only one study (Ref. 29) was available in Sweden, the Netherlands and Finland. The results were the same, but Sweden did not accept the study because very basic background information was lacking. The Netherlands classified study 29 to "category 3": the study was included in the conclusions only because no data in "category 1 and 2" were available. Sweden also rejected study 30 on the basis of lacking background information.

The same algae inhibition growth test was available in Sweden, Finland and the Netherlands (Ref. 33), and the same result was given. Sweden questioned the result because of some deficiencies, but accepted the study.

Although countries gave same results for the acute toxicity tests, Finland considered iprodione toxic to water organisms, Sweden moderately or highly toxic, and the Netherlands moderately toxic to fish and crustaceans and slightly toxic to algae. Obviously, the countries had different toxicity classifications.

Beneficial insects, non-target species

Only Finland and Sweden had a study concerning toxicity to earthworms (Ref. 34). Both countries stated that no mortality was discovered in the study.

Six bee toxicity tests were submitted to Sweden (Ref. 35-40). Three of those studies were not presented at all (Ref. 38: only a list considering toxicity of pesticides to bees; Ref. 39: same study as ref. 36; Ref. 40: all the products are not approved in Sweden). Three of the studies were available in Finland (Ref. 35-37) and one also in the Netherlands (Ref. 35). Those studies were conducted with different products, using different application methods and concentrations. The results in the reviews were shown in different ways and were very confusing. On the basis of properties of iprodione all the countries considered iprodione slightly toxic to bees, but the final conclusions were conflicting: Finland stated iprodione as not hazardous to bees, the Netherlands classified iprodione not-dangerous given a favourable ratio between the dosage per ha and the toxicity in bees, but Sweden assessed that it was dangerous to bees to spray iprodione-containing products.

Conclusions

Forty different studies were selected to the comparison in Pilot Project Phase 3. Two of the studies (5%) were available in all the countries, 10 (25.0%) in three of the participating countries, 16 (40.0%) in two countries and 12 (30%) only in one country.

Sweden and Finland had in most cases the same documentation. Also the Netherlands had many of the same studies as the Nordic countries. But only a few of the studies reviewed in the US were the same as in Europe.

The US evaluated the studies very accurately and the studies were perhaps rejected more easily than by the other participating countries. Sweden went through the studies carefully and rejected many studies because of their deficiencies. Both the US and Sweden clearly explained the deficiencies of the studies and the unacceptability of those studies. The Netherlands showed only in the references which studies were not accepted in the conclusions. Finland criticized the studies, but obviously accepted them in spite of the deficiencies. The US calculated some results of their own.

In most cases, the presented results of the individual studies were the same in all the countries. Also the final conclusions were similar. Finland and Sweden emphasized the degradation rate of iprodione and assumed that the substance might be found remaining in soil after another growing season. The main differences were in dealing with toxicity to bees and birds. The reviews represent different phases of the hazard/risk assessment procedure which may explain the different conclusions.

2.4 Potential for use of reviews by other countries in lieu of conducting a separate review

All the reviews concerning iprodione were of relatively good quality. The Swedish report was written in accordance with the Nordic recommendations and therefore it is possible to use it in lieu of conducting a separate review at least in the Nordic countries. Also the Dutch review can be used to a great extent, except that in the reviews of the Nordic countries more attention must be paid to the impact of the northern environmental conditions on the fate and effects of a pesticide.

The US review was reported in great detail, but it is a little difficult to use it (and also to judge it) because only a few separate reports were available. Any hazard or risk assessment was not included in the review. However, it is of quality and could be used at least as supporting evaluation.

The criteria specified below can be used for determining when data reviews by others can be accepted:

- The data review should contain a detailed enough reference list. On the basis of the reference list it should be easy to find out if you have the same studies in your own data package.

- The studies should be reported in sufficient detail. Reporting could be handled in the same way as Sweden goes through the studies: first study performance is presented, then the results and finally the comments.

  All the essential background information and description of the method should be provided. But if the study has been conducted in accordance with a well known test

guideline it is not necessary to describe the study performance in detail. In that case it is sufficient to mention the test guideline and the deviations, if any.

Results should be reported as values but can partially be shown in tables. If the results are also classified with words, the classification system must be presented or referred to.

Comments on the deficiencies discovered in studies should be specified study by study. The US and Sweden did so very clearly in their reviews.

• Acceptance of the studies should be clearly indicated and the rejection reasons should be mentioned. The US listed in order and in detail all the rejection reasons. At same time it would be useful to mention which additional studies are required. This would bring us one step nearer to harmonization of the study requirements.

It is not necessary to give a final risk assessment of the substance because the product usually has not been used for the same applications in different countries.

2.5 Recommendations

Countries could increasingly use each other's pesticide evaluations if improvements are made in the following areas. The improvements could proceed in two phases:

Phase 1:

There is a need for **guidelines on how to report individual studies** ("OECD Guidelines for Assessing of Chemical Test Report"). The guidelines should include detail advice, about the minimum relevant information that should considered in the study reports. The purpose is that a reader gets a reliable idea of the study without looking the original study.

The guidelines should also include advice about when an individual study should be rejected and the minimum validity terms. The study report should clearly state whether or not the study was accepted.

Detailed advice about how to make a reference list should also be included in the guidelines. This should cover for example, the study title, authors, number and date of the report, pages.

Phase 2:

It would be useful to have **guidelines on how to write a hazard assessment report concerning ecotoxicological and toxicological effects of a pesticide** ("OECD Guidelines for Writing a Chemical Evaluation Report"). The guidelines should list all study areas (introduction, physical-chemical properties, toxicology, environmental fate, ecotoxicology, summaries, hazard assessment) and how they should be handled. Risks of a pesticide need

not to be described in the review because uses, dosages, use applications, environmental conditions etc. usually vary country by country. Countries could make the final risk assessment themselves on the basis of an internationally accepted hazard assessment review.

One possibility for sharing the burden of pesticide re-registration would be to write individual study sheets according to a given guideline. A separate hazard assessment report could be prepared on the basis of these study sheets. Newly received studies are reported study by study but the hazard assessment would be rewritten only if the results of the supplementary studies changed the previous hazard assessment report.

The final risk assessment could be done country by country on the basis of an internationally accepted hazard assessment report.

Other proposals to improve evaluation of pesticides:

- There is a need for internationally accepted hazard and risk assessment procedures.

- There is a need for internationally accepted calculation models to predict environmental concentration.

- The terminology of hazard identification, hazard and risk assessment should be determined.

- More attention should be paid to test guidelines development in order to have guidelines for bee toxicity and soil degradation tests.

- More attention should be paid to GLP when studies are reviewed.

- Recommendations are needed as to the proper way of setting a NOEL-value in studies concerning the effects of a substance on terrestrial and aquatic organisms.

Appendices on environmental fate and ecotoxicology

Appendix 1. REFERENCES I

Environmental fate and ecotoxicology studies of iprodione organized by study type

STUDY TYPE	FIN	SWE	NL	US
FATE AND BEHAVIOUR IN THE ENVIRONMENT				
Hydrolysis				
1. Laurent, M., Buys, M. & Chabassol, Y. 1976: RP 26019 - Degradation in water. Rhone-Poulenc Report R.P./RD/CNG-An No. 3036. 10 Sep 1976.	X	X	X	
2. RP 26 019 Degradation in water. Addendum to RP/RD/CNG-An-Report No 3036. RP/RD/CNG-An-No 3438. September 1976.		X		
3. Laurent, M. & Buys, M. 1974: RP 26019 solubility and stability in water. Rhone-Poulenc S.U.C.R.P. - D.S.An.Nord. No. 2585. 21 Oct 1974.	X	X		
4. Das, Y. T. 1990: Hydrolysis of (Phenyl(U)-^{14}C)iprodione in aqueous solutions buffered at pH 5,7 and 9. ISSI Laboratory Project No. 89100. Rhone-Poulenc Study No. EC-89-050. Unpublished study performed by Innovative Scientific Services, Inc., Piscataway, NJ, and submitted by Rhone-Poulenc Ag Company, Research Triangle Park, NC.				X
Photodegradation in water				
5. Laurent, M., Buys, M. & Chabassol, Y. 1977: RP 26019 - Photo-degradation in water. Rhone Poulenc Report R.P./R.D./C.N.G.-An. No.3223. 26 Jul 1977.	X	X		
6. RP 26019 Kinetics in the degradation in solution exposed to ultra-violet radiation. SUCRP - DS An Nord No 2536-E. Sept 1974.		X		
7. Adrian, P. P. & Robles, J. 1991: ^{14}C-Iprodione aqueous pholysis. Laboratory Project ID: Study No. 90-22. Filing reference: AG/GRLD/AN/9115524. Unpublished study performed by Rhone-Poulenc.				X
Soil metabolism				
8a. International Bio-Test Laboratories Inc. 1977: Microbiological tests to define activities of RP 26019 on selected and naturally occuring soil microflora. IBT Report No. 8536-11033. 22 Dec 1977.	X			
8b. Degradation of RP 26019 in the soil. Treatment at 1 and 10 ppm with phenyl ^{14}C labelled material. RP/RD/CNG and CNG An No 19320-E. August 1977		X		
8c. Gouot et al. Dégradation du 26019 RP dans le sol - traitements avec 1 ou 10 ppm fungicide à l'aide de 26019 RP marqué au ^{14}C (Unpublished literature of Rhone-Poulenc Industries provided by Agriben Nederland BV, report nr. 19320			X	
9a. Biospherics Incorporated 1978: ^{14}C Iprodione microbial metabolism in soil. Report No. 5-78-12. 3 Nov 1978.	X			
9b. ^{14}C Iprodione microbial metabolism in soil. Biospherics Incorporated No 5-78-12, November 3, 1978.		X		
10. Degradation of RP 26019 in the soil. Treatment with 2 and 5 ppm of ^{14}C labelled product. Final report. RP/RD/CNG No 18785 du 31 août 1976.		X	X	

STUDY TYPE	FIN	SWE	NL	US
Biodegradation in aquatic systems				
11. Borriston Laboratories Inc. 1982: Aquatic matabolism of ^{14}C - RP 26019. Borriston Project No. 3-2201. 31 Aug 1982.	X	X	X	X
12. Borriston Laboratories Inc. 1983: Anaerobic aquatic metabolism of ^{14}C - RP 26019. Borriston Project No 3-2202. 9 Feb 1983.	X	X	X	X
13. Biodegradability of iprodione according to OECD Guideline 301 B (Modified Sturmtest). TNO Division of technology for society No R 88/427, 1989-01-16.		X		
14. Van Buijsen, H.J.J. 1987: Biodegradation of RP 30228 in an aerobic water/sediment system. Unpublished literature of MT-TNO provided by Agriben Nederland BV, report nr. R 87/253.		X	X	
Adsorption				
15. Williams, C. M: 1990: Iprodione Sorption Study in Soil. May & Baker Ltd. D. Ag. 1451, May 1990.	X	X		
Mobility and leaching				
16. Lacroix, L., Gouot, J.M., Laurent, M. & Buys, M. 1975: RP 26019 leaching study in soils. Rhone-Poulenc, RP/RD/CNG and CNG-An. No. 18173.8 Apr 1975.	X	X		
17. A study to investigate the leaching of RP 29019 in soil, using ^{14}C-labelled RP 26019. RP/RD/CNG and CNG-An No 18845-E, Oct 1976.		X	X	
ECOTOXICITY				
Avian testing				
18. McGinnis Jr., C.H. 1973: The determination of the acute oral LD_{50} in bobwhite quail for RP 26019. Hess & Clark Report. CHM 73:93. 3 Dec 1973.	X	X	X	
19. McGinnis Jr., C.H. 1974: The determination of the acute oral LD_{50} mallard ducks for RP 26019. Hess & Clark Report No. CHM 74:49. 8 May 1974.	X	X	X	
Dietary				
20. McGinnis Jr., C. H. 1974: The effects of dietary RP 26019 and technical dieldrin on young mallard ducks. An 8 day subacute toxicity test. Hess & Clark Research Report No. CHM 74:64. 9 Jul 1974.	X	X	X	
21. Wildlife International Ltd. 1980: Subacute feeding - reproduction. Screening bioassay - bobwhite quail. Iprodione technical. Final Report. 6 Aug 1980.	X			
22. McGinnis Jr., C.H. 1974: The effect of dietary 26019RP on body weight, feed consumption, reproduction and the production of RP 26019 residues in body tissues and eggs of bobwhite quail. Hess & Clark Research Report No. CHM 74:105. 29 Oct 1974.	X			
23. The effects of dietary RP 26019 and technical dieldrin on young bobwhite Quail - A 12 day subacute toxicity test. Hess & Clark, Research Department No CHM 74:14. 12 Feb 1974.		X		
AQUATIC TESTING				
Fish, acute toxicity				

STUDY TYPE	FIN	SWE	NL	US
24. Industrial Bio-Test Laboratories Inc. 1974: Four-day static fish toxicity studies with RP 26019 technical in rainbow trout, bluegills and channel Catfish. IBT No. 621-05132. 12 Jun 1974.	X	X	X	
25. Union Carbide Environmental Services 1978: The acute toxicity of RP 26019 technical to the rainbow trout Salmo gairdneri Richardson. UCES Proj. No. 11506-48-03. 31 May 1978.	X	X		
26. Union Carbide Environmental Services 1978. The acute toxicity of RP 26019 technical to the bluegill sunfish Lepomis macrochirus Rafinesque. UCES Proj. No. 11506-48-02. 31 May 1978.	X	X		
27. Analytical Bio-Chemistry Laboratories, Inc. 1986: Acute flow-through toxicity of iprodione technical to channel catfish (Ictalurus punctatus). Report No. 34385. 17 Jul 1986.	X	X		X
28. Surprenant, D. C. 1988: Acute toxicity of iprodione technical to sheepshead minnow (Cyprinodon variegatus) under flow-through conditions. Springborn Life Sciences, Inc. Study Report No. 87-11-2583. 5 Jan 1988.	X	X		
Daphnia, acute immobilization				
29. Ambrosi, D., Desmoras, J. & Lacroix, L. 1976: Fungicides - Toxicity of RP 26019 to Daphnia (Daphnia pulex). Rhone-Poulenc R.P./R.D./C.N.G. Report No. 18940. 21 Dec 1976.	X	X	X	
30. Ambrosi, D., Desmoras, J. & Lacroix, L. 1977: Fungicides - Toxicity - Toxicity of RP 26019 to Daphnia (Daphnia magna). Rhone-Poulenc R.P./R.D./C.N.G. Report No. 19168. 3 Jun 1977.	X	X		
31. The Acute toxicity of RP26019 technical to the water flea Daphnia magna Strauss. Union Carbide Environmental Services, UCES Project No 11506-48-01. 5 Dec 1977.		X		
32. 48-hour static LC_{50} of RP26019 technical in Daphnia magna. Cannon Laboratories Inc., Laboratory No 7E-8445, 19 Oct, 1977.		X		
Algae, growth inhibition				
33. Oldersma, H., Hantsveit, A.O. & Pullens, M.A.H.L. 1984: The effect of the product iprodione (26019RP) on the growth of the alga Scenedesmus subspicatus. Netherlands Organization for Applied Scientific Research. Report No. R84/180. 8 Nov 1984.	X	X	X	
Beneficial insects, non-target species **Earthworm, acute toxicity**				
34. Roark, J.H. & Dale, J.L. 1979: The effect of turf fungicides on earthworms. Arkansas Academy of Science Proceedings, vol. XXXIII, 1979. 71-74.	X	X		
Acute toxicity to honeybee				
35. Twinn, D.C. & Lacy, J.C.1975: Fungicides -26019RP, laboratory determination of honeybee toxicity. UK 1974. May & Baker Ltd. Report No. AR993. March 1975.	X	X	X	
36. Lacy, J.C. & Twinn, D.C. 1983: Fungicide iprodione - laboratory honey bee direct contact toxicity of Rovral Flo and its formulation without iprodione. May & Baker Ltd. Report No. R.A.G.86. August 1983. (FIN, SWE)	X	X		

STUDY TYPE	FIN	SWE	NL	US
37. Lacy, J.C. & Twinn, D.C. 1981: Fungicides - iprodione: EXP 1861. Laboratory determination of honeybee contact toxicity. UK 1981. May & Baker Ltd. Report No. R.Ag. 31 December 1981.	X	X		
38. Toxicity of pesticides and other agricultural chemicals to honey bees. Laboratory studies. University of California - Agricultural Extension, service M 16 (1967).		X		
39. The safety to honeybees of an iprodione-phosalone tank mix applied to flowering winter oilseed rape. Applied Biology 6, 1984 p. 311-321.		X		
40. Insecticide, fungicide: Zolone Flo/Rovral Flo Mixture. Laboratory honeybee direct contact toxicity. UK 1983. May & Baker Ltd. No R Ag 110, September 1983 (SWE)		X		

Appendix 2. REFERENCES II

Studies of iprodione on environmental fate and ecotoxicology organized in alphabetical order

26019 RP Kinetics in the degradation in solution exposed to ultra-violet radiation. SUCRP - DS An Nord No 2536-E. Sep 1974.

48-hour static LC_{50} of RP26019 technical in Daphnia magna. Cannon Laboratories Inc., Laboratory No 7E-8445, 19 Oct, 1977.

A study to investigate the leaching of 29019 RP in soil, using ^{14}C-labelled 26019 RP. RP/RD/CNG and CNG-An No 18845-E, Oct 1976.

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Ambrosi, D., Desmoras, J. & Lacroix, L. 1976: Fungicides - Toxicity of RP26019 to Daphnia (Daphnia pulex). Rhone-Poulenc R.P./R.D./C.N.G. Report No. 18940. 21 Dec 1976.

Ambrosi, D., Desmoras, J. & Lacroix, L. 1977: Fungicides - Toxicity - Toxicity of RP26019 to Daphnia (Daphnia magna). Rhone-Poulenc R.P./R.D./C.N.G. Report No. 19168. 3 Jun 1977.

Analytical Bio-Chemistry Laboratories, Inc. 1986: Acute flow-through toxicity of iprodione technical to channel catfish (Ictalurus punctatus). Report No. 34385. 17 Jul 1986.

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Biospherics Incorporated 1978: ^{14}C Iprodione microbial metabolism in soil. Report No. 5-78-12. 3 Nov 1978. ?? Iprodione microbial metabolism in soil. Biospherics Incorporated No 5-78-12, November 3,1978.

Borriston Laboratories Inc. 1982: Aquatic matabolism of ^{14}C - RP 26019. Borriston Project No. 3-2201. 31 Aug 1982.

Borriston Laboratories Inc. 1983: Anaerobic aquatic metabolism of ^{14}C - Rp 26019. Borriston Project No 3-2202. 9 Feb 1983.

Das, Y. T. 1990: Hydrolysis of (Phenyl(U)-^{14}C)iprodione in aqueous solutions buffered at pH 5,7 and 9. ISSI Laboratory Project No. 89100. Rhone-Poulenc Study No. EC-89-050. Unpublished study performed by Innovative Scientific Services, Inc., Piscataway, NJ, and submitted by Rhone-Poulenc Ag Company, Research Triangle Park, NC.

Degradation of RP 26019 in the soil. Treatment at 1 and 10 ppm with phenyl ^{14}C labelled material. RP/RD/CNG and CNG An No 19320-E. August 1977

Degradation of RP 26019 in the soil. Treatment with 2 and 5 ppm of 14c labelled product. Final report. RP/RD/CNG No 18785 du 31 aout 1976.

Gouot et al. Dégradation du 26019 RP dans le sol-traitements avec 1 ou 10 ppm fungicide à l'aide de 26019 RP marqué au ^{14}C (Unpublished literature of Rhone-Poulenc Industries provided by Agriben Nederland BV, report nr. 19320.

Industrial Bio-Test Laboratories Inc. 1974: Four-day static fish toxicity studies with RP 26019 technical in rainbow trout, bluegills and channel Catfish. IBT No. 621-05132. 12 Jun 1974.

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Lacroix, L., Gouot, J.M., Laurent, M. & Buys, M. 1975: RP 26019 leaching study in soils. Rhone-Poulenc, RP/RD/CNG and CNG-An. No. 18173.8 Apr 1975.

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Oldersma, H., Hantsveit, A.O. & Pullens, M.A.H.L. 1984: The effect of the product iprodione (26019RP) on the growth of the alga Scenedesmus subspicatus. Netherlands Organization for Applied Scientific Research. Report No. R84/180. 8 Nov 1984.

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RP 26 019 Degradation in water. Addendum to RP/RD/CNG-An-Report No 3036. RP/RD/CNG-An-No 3438. September 1976.

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The effects of dietary 26019RP and technical dieldrin on young bobwhite Quail - A 12 day subacute toxicity test. Hess & Clark, Research Department No CHM 74:14. 12 Feb 1974.

The Acute toxicity of RP26019 technical to the water flea Daphnia magna Strauss. Union Carbide Environmental Services, UCES Project No 11506-48-01. 5 Dec 1977.

The safety to honeybees of an iprodione-phosalone tank mix applied to flowering winter oilseed rape. Applied Biology 6, 1984 p. 311-321.

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Union Carbide Environmental Services 1978. The acute toxicity of RP 26019 technical to the bluegill sunfish Lepomis macrochirus Rafinesque. UCES Proj. No. 11506-48-02. 31 May 1978.

Van Buijsen, H.J.J. 1987: Biodegradation of RP 30228 in an aerobic water/sediment system. Unpublished literature of MT-TNO provided by Agriben Nederland BV, report nr. R 87/253.

Wildlife International Ltd. 1980: Subacute feeding - reproduction. Screening bioassay - bobwhite quail. Iprodione technical. Final Report. 6 Aug 1980.

Wildlife International Ltd. 1981: One-generation reproduction study - bobwhite quail - iprodione technical. Final Report. 31 Mar 1981.

Wildlife International Ltd. 1981: One-generation reproduction study - mallard duck - iprodione technical. Final Report. 20 Mar 1981.

Williams, C. M: 1990: Iprodione Sorption Study in Soil. May & Baker Ltd. D. Ag. 1451, May 1990.

Appendix 3. Table 1

IPRODIONE: FATE AND BEHAVIOUR IN THE ENVIRONMENT

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	HYDROLYSIS					
1. *2.	Hydrolysis in buffered solutions, [1]pH 3, [2]pH 6, [3]pH 9, 24 °C, 35 days	DT_{50}	[1] not degraded [2] 20 days [3] completely in 24 hours	[1] > 35 days [2] 20 days [3] < 1 day	[1] > 35 days [2] 20 days [3] < 1 day	
3.	Hydrolysis in buffered solutions, [1] pH 4 [2] pH 5 [3] pH 6 [4] pH 7 [5] pH 9	DT_{50}	[1] not degraded [2] 3 months [3] 20 days [4] 24 hours [5] < 1 hour	[1] not degraded °(1 year) [2] 3 months °(3 months) [3] 20 days °(20 days) [4] 1 day °(2-3 days) [5] 1 hour		
4.	Hydrolysis in aqueous buffered solution pH 5, pH 7, [1]pH 9	DT_{50}				[1]4.7 days
	PHOTODEGRADATION IN WATER					
5.	Photodegradation in buffered aqueous solution, pH 3, 25 °C	DT_{50}	100 hours	100 hours **After 187 hours 27% a.i; 18% CO_2; 34% unknown and 14% known metabolites of the original radioactivity		
6.	Photodegradation			The study was only mentioned in the references, but not reported or taken into account in the conclusions		
7.	Photolysis of [14]C-Iprodione in citric acid buffered solution, pH 5, 25 °C, 33 days	DT_{50}				67 days Major degradation product RP 30228

* Only Sweden had that extra study
** Two parts of the same study had been reported in the Swedish review
° It showed own values in the Swedish review

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	SOIL METABOLISM					
8a. 8b. 8c.	[1]Aerobic and [2]anaerobic degradation of ^{14}C-iprodione in clay loam (pH 7.0, OM 4.0%), 25 and 15 °C, silty clay loam (pH 7.6, OM 3.1%), 13 months	DT_{50} (days) Degradation products	Clay loam: [1]50-70 (25 °C), [2]20-30 (25 °C), [1]160 (15 °C) Silty clay loam: [1]20 (25 °C)	Clay loam: [1]50-70 (25 °C), [2]20-30 (25 °C), [1]160 (15 °C) Silty clay loam: [1]20 (25 °C)	DT_{50}: Clay loam: [1]50-70 (25 °C), [2]20-30 (25 °C),[1]160 (15 °C) Silty clay loam: [1]20 (25 °C) DT_{90}: Clay loam: [1]213-250 (25 °), [1]> 385 (15 °C), [2]113-130 (25 °C) Silty clay loam: [1]100 (25 °C)	
9a. 9b.	Degradation of ^{14}C-iprodione in [1]loam (pH 5.8, OM 6.5%), [2]sandy loam (pH 5.2, OM 1.3%), 25 °C, 4 weeks	Recovered fractions of original radioactivity at the end of the study	49-93% iprodione, 3.8-38% RP 30228	49-93% iprodione, 3.8-38% RP 30228, CO_2 not evaporated		
10.	[1] Aerobic and [2]anaerobic degradation in loam (pH 7.3, OM 4.1%) 23-25 °C, 13 months	DT_{50} (days)		[1]30-35 days [2]50-55 days RP 30228: DT_{50} > 300 days	DT_{50}:[1] > 33, [2]60, [1]30 days DT_{90}: [2] > 113, [1]165-200 days	
	BIODEGRADATION IN AQUATIC SYSTEMS					
11.	Degradation of ^{14}C-iprodione in natural water (pH 6.7) 23 °C, 30 days	DT_{50} (days) Recovered fractions of original radioactivity at the end of the study	RP 30228 96%, < 0.2% evaporated, undecomposed iprodione and other residual products < 4%	2.9 days CO_2 < 0.1%, iprodione 1.2 %, RP 30228 95.9%, unidentified products 3.0%	DT_{50}: 2.9 days DT_{90}: 15 days < 0.2% evaporated	2.9 days < 0.2% evaporated
12.	Anaerobic degradation of ^{14}C-iprodione in water (pH 6.7)-sediment (pH 7.9)system, 22 °C, 184 days	DT_{50} (days)	6.4 days in water and 126 days in the whole system	6.4 days in water and 126 days in the whole system	6.4 days in water and 126 days in the whole system	6.4 days in water and 126 days in the whole system
13.	Ready biodegradability test, 20 °C, 28 days			71-87% of the original radioactivity degradated. CO_2 0.1-0.2%		
14.	Degradation of ^{14}C- and unlabelled RP 30228 in ditch water (pH 7.7, OM 7.1%), 20 °C, 84 days	DT_{50} (days)		84 days After two weeks almost no changes occurred in ratio between r.a. found in water and sediment. At the end bound residue 10%, CO_2 1%	> 84 days After two weeks almost no changes occurred in ratio between r.a. found in water and sediment. At the end bound residue 10%, CO_2 1%	

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	ADSORPTION					
15.	Adsorption of ^{14}C-iprodione,clay loam, OM 4.6% pH 6	K_{oc}	1323 Desorption 1951-2842	1320 K_d 44.9 - 71.9		
	MOBILITY AND LEACHING					
16.	Soil column study in tree soils: pH 5.1-7.4, OM 1.8-41%, 200 mm precipit. 48 hours, 50% Iprodione product	Growth inhibition of spores of Bothytris cinerea	Growth was inhibited to 10 cm depth. 0.005-0.01 mg/l iprodione was found filtration water	Effects were not discovered deeper than 10 cm from the soil surface or in the filtration water		
17.	A. Soil column study of ^{14}C-iprodione in 4 soils: pH 5.7-7.8, OM 1.6-4.0%, 500 mm precipit. 24-30 h			0.5-1.9% of the original radioactivity in the filtration water and 95% in the 15 cm surface soil	0.5-1.9% of the original radioactivity in the filtration water and 71% in the 15 cm surface soil $0.08 \leq R_f(\text{column}) \leq 0.14\%$ K_{om} -values: 82-206 dm^3/kg	
	B. Aged leaching soil column study: 30 days incubation in 25 °C, 500 mm precipitation 24-30 h			50% of the original radioactivity was recovered after incubation. Metabolites: RP 30228 (mainly in the 0-5 cm layer), RP 36221	0.2-1.7% leached. Radioactivity was mainly recovered in the 0-5 cm layer. Metabolites: RP 30228 (mainly in the 0-5 cm layer), RP 36221 (small amounts)	

Appendix 4. Table 2

IPRODIONE: ECOTOXICITY

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	AVIAN TOXICITY					
18.	Acute, oral toxicity of technical iprodione to Colinus virgianus 300-1370 mg/kg (*bw)	LD_{50} (6 days) mg/kg (bw)	930	930	930	
19.	Acute oral toxicity of iprodione to Anas platyrhynchos 410-4800 mg/kg (bw)	LD_{50} (5 days) mg/kg (bw)	> 10 400	no values given	> 10400	
	AVIAN DIETARY TOXICITY					
20.	Subacute toxicity to Anas platyrhynchos 20 000 mg/kg (**fw)	LC_{50} (5 + 3 days) mg/kg (fw) Body weight and food consumption	Not a single bird died -> LC_{50} not assessed	No mortality NOEC 20 000 mg/kg	> 20 000	
21.	Subacute toxicity of iprodione to Colinus virgianus 562-5620 mg/kg (fw)	LC_{50} (8 weeks) mg/kg (fw) Weight, food consumption, egg production	No differences in mortality between treatments and control. Changes in weight, food consumption and egg production was observed.			
22.	Subacute toxicity of iprodione to Colinus virgianus 13,31,114 mg/kg (fw)	Weight, food consumption, egg production and fertilization were assessed	No changes between controls and treatments			
23.	Subacute toxicity of iprodione to Colinus virgianus	LC_{50} (5 + 7 days) mg/kg (food weight) Food consumption		9200		

* bw = bird weight
** fw = food weight

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	ACUTE TOXICITY TO FISH					
24.	Acute toxicity of iprodione to [1]Salmo gairdneri, [2]Lepomis macrochirus, [3]Ictalurus punctatus	LC_{50} (92 h) mg/l	[1]6.7 [2]2.25 [3]2.63	Study has not been accepted	[1]6.7 [2]2.25 [3]2.63	
25.	Acute toxicity of iprodione to Salmo gairdneri pH 7.2, 12 °C	LC_{50} (96 h) NOEC mg/l	4.2 Not mentioned	4.2 1.8		
26.	Acute toxicity of iprodione to Lepomis macrochirus pH 7.3, 23 °C	LC_{50} (96 h) NOEC mg/l	4.2 Not mentioned	6.3 1.0		
27.	Acute toxicity of iprodione to Ictalurus punctatus pH 8-8.2, 22 °C	LC_{50} (96 h) NOEC mg/l	3.1 Not mentioned	3.1 0.52		3.1 Not mentioned
28.	Acute toxicity of iprodione to Cyprinodon variegatus pH 7.9, 22°C, 31% salinity	LC_{50} (96 h) NOEC mg/l	7.7 < 2.2	7.7 < 2.2		
	DAPHNIA, IMMOBILIZATION TEST					
29.	Acute toxicity of [1]technical iprodione, [2]Rovral 50% WP to Daphnia pulex	LC_{50} (72 h) mg/l	[1]3.6 [2]5.9	[1]3.6 [2]not assessed	[1]4.7 [2]5.9	
30.	Acute toxicity of [1]iprodione, [2]Rovral 50 WP to Daphnia magna	LC_{50} (72 h) mg/l	[1]4.0 [2]5.8	[1]4.0 [2]not assessed		
31.	Acute toxicity of iprodione to Daphnia magna pH 7.3-7.7, 17±1 °C	LC_{50} (48 h) NOEC mg/l		7.2 < 3.2		
32.	Acute toxicity of iprodione to Daphnia magna pH 7.5, 17±1 °C	LC_1 LC_{50} mg/l		0.044 0.43		
	ALGAE, GROWTH INHIBITION					
33.	Effects of iprodione on the growth of Scenedesmus subspicatus, 20 °C	EC_{50} (96 h) NOEC mg/l	15.3 3.2	15.3 3.2	15.3 3.2	

Ref	STUDY AREA	ENDPOINT	FIN	SWE	NL	US
	BENEFICIAL INSECTS, NON-TARGET SPECIES					
34.	Acute toxicity of [1]iprodione, [2]50% product to Eisenia foetida	Mortality Reproduction weekly during 84 days	No differences in mortality and reproduction between treatments and control	No effects		
35.	Contact and oral acute toxicity of [1]iprodione, [2]50% product, [3]20% EC product to Apis mellifera	LD_{50}, LC_{50}	[1]Oral toxicity > 1000 a.i. µg/bee [1,2,3]Contact > 400 a.i. µg/bee	[1]Contact < 4% mortality; [1]topical application 0%; [2,3]Not assessed	Contact LC_{50} (48 h) [1,2,3] > 5 g/l [1]Topical application LD_{50} (48 h) > 400 µg/bee Oral LC_{50} (144 h) [1] > 5 g/l, [2] 5.0 g/l	
36.	Contact toxicity of Rovral FLO (a.i. 25%) to honey bees Treatments: 0.05-4.0%	Mortality % (24 h)	0.05% iprodione -> 0% mortality 0.5% -> 39% 0.7% -> 81% 1.5-4.0 -> 100% LC_{50} not determined	0.2% iprodione -> 1% mortality 0.3% -> 23% 0.7% -> 81% 1.5-4.9% -> 100%		
37.	Contact toxicity of iprodione products [1]Exp 1861, [2]Rovral 50% WP	Mortality % (24 h)	[1]0.075% -> 0% mortality [1]0.6% -> 40% [1]2.4% -> 100% [2]2.4% -> 15%	[1]0.3% -> 0% mortality [1]1.2% -> 88% [1]2.4% -> 100% [2]Not assessed		
38.	Toxicity to bees			Study has not been accepted		
39.	Toxicity to bees			Study has not been accepted		
40.	Toxicity to bees			Study has not been accepted		

ANNEX 7

PHASE 3 REPORT

ON

PYRIDATE

Lead Country: The Netherlands

Contents

Summary

This report is the Dutch contribution in the Pilot Project of OECD's Pesticide Program. The Netherlands acted as lead country for pyridate for the comparison of data reviews done by six countries: including Australia, Canada, Germany, Switzerland, the Netherlands and the United States.

The lay-out of reviews is compared and it is shown that of all participating countries only the Netherlands summarize all studies on toxicology and ecotoxicology individually. Of all references of all countries together, only 61 out of 372 references were reviewed by two or more countries. From the common studies the countries always established the same endpoints. For some studies different final fate and effect results were reported. In all cases, however, the differences were small.

It can be concluded that it seems possible for countries to use reviews prepared by other countries for establishing their own results. Standardization would be important for several subjects e.g.

- items that should be available in the summary
- units (SI-system)
- classifications
- literature references
- format.

1 Introduction

One of the 7 substances chosen in the Pilot Project in the framework of OECD's Pesticides Program was pyridate. The Netherlands acted as lead country for the comparison of data reviews done by the participating countries. The following countries contributed their data reviews of pyridate:

- Australia
- Canada
- Germany
- Switzerland
- The Netherlands
- United States.

The study disciplines for pyridate include the following more specific contributions of the participating countries:

- **Product chemistry:**
  Australia, Canada, Germany, the Netherlands, the United States

- **Toxicology and metabolism:**
  Australia, Canada, Germany, the Netherlands, the United States

- **Fate and behaviour in the environment:**
  Australia, Canada, Germany, the Netherlands, the United States

- **Ecotoxicology:**
  Australia, Canada, Germany, the Netherlands, the United States

Due to legal restrictions it was not possible for Switzerland to deliver the data reviews. Switzerland publishes only the registration decision taken by the government.

The areas to be covered for pyridate are:

- acute toxicity
- subchronic toxicity, only oral dog, one year
- developmental and reproductive toxicity
- chronic toxicity
- soil metabolism, aerobic and anaerobic, in representative soils
- mobility/leaching in representative soil types and mobility of metabolites and breakdown products
- avian acute oral LD_{50}
- avian dietary toxicity LC_{50} - terrestrial bird (short-term)
- avian dietary toxicity LC_{50} - aquatic bird (short-term)
- avian reproduction test - terrestrial bird
- avian reproduction test - aquatic bird
- fish acute toxicity LC_{50}, freshwater: warmwater species
- fish acute toxicity LC_{50}, freshwater: coldwater species

- Daphnia acute immobilization test
- aquatic bioavailability, biomagnification, bioaccumulation
- acute toxicity to honey bees (LD_{50})
- earthworm, acute toxicity test
- algae growth inhibition.

These areas were chosen because of some different interpretation between the participating countries or because harmonization did not seem problematic (all acute studies).

2 Types of data reviews

The types of data reviews are summarized in Appendix 1.

The Netherlands, Australia, Canada and the US describe almost all individual studies in each study category provided for toxicology. Germany is the only country which describes all of the data reviews for each study category in one document. For the ecotoxicology, the Netherlands is the only country that describes all individual studies in each study category. Australia and Canada compile data reviews for each study category and Germany and the US review data for the test areas.

The reviews of Australia, Canada and the Netherlands are most clear. All studies are described in the same way. The Netherlands uses a prescribed computer format. The reviews of the US consist each of 3 or 4 sheets in which the studies are described. All these reviews are provided loose, not bound. The review of the Germans is short, the studies are either not described individually, or are described very briefly.

All reviews have a length of 50 pages or more. This includes toxicology and ecotoxicology together. The toxicology part of all countries except the Netherlands is more extensive than the ecotoxicology part. All reviews are written in English and contain a summary also written (or translated) in English. All summaries included conclusions of the reviewer about inherent toxicity.

From the provided data it is shown that only the reviews of the Netherlands and sometimes the reviews of the US contain information on the quality of the data. Furthermore, the ecotoxicology part of the Netherlands has its own quality index, consisting of 4 categories.

None of the countries describe in their review whether the studies are performed according to GLP. For the Netherlands we can say that the studies should be performed under GLP if the study is performed after July 1, 1992.

3 Comparison of values/results reported in the data reviews

From all references of the countries together (372), 61 studies were reviewed by two or more countries. These studies are taken up in a new reference list (see appendix 2). It is likely that there is more overlap in studies reviewed than indicated on this list, because reviewers cited the studies in different ways (e.g. title and authors of the reports sometimes vary. Not all countries use report numbers or study numbers in their reference list. Therefore it is difficult to compare the references.

From the common studies (see appendix 3) the different countries always established the same endpoints. For some studies different final fate and effect data were reported. In all cases there were only small differences. See the discussion below. It should be remarked there are no reviews available from Switzerland.

3.1 Human toxicology

In the evaluation of human toxicological data no clear differences can be found between the various countries.

Acute toxicity

For some acute studies some countries gave the LD_{50} as '>' the highest dose level, while other countries calculated the LD_{50}. For example, for reference 1 (NL, CND, D), acute oral mouse, the Netherlands and Germany gave a '>' result, while Canada calculated the result.

For reference 5 (NL, US), acute oral rat, the Netherlands gave the results in mg/kg b.w., while the US gave the results in ml/kg. This is difficult to compare. It is not clear why there is such a big difference for the dermal LD_{50} value (reference 7, NL, CND, D), but this difference is not very important because all values are above the highest hazard classification. The eye irritation studies are difficult to interpret because it is not known which classification is used. For the eye irritation study (reference 10, NL, AUS, CND, D, US) the Netherlands and Australia classified pyridate as "irritating" and "moderate", while Canada called it "mild" and Germany and the US classified it "not irritating". The formulation Lentagran WP was classified as "irritating" by the Netherlands and "mild" by Canada. For the skin irritation studies the classification methods are also not known, but all countries came up with similar classifications. For reference 12, the Netherlands, Australia, Canada, Denmark and the United States all arrived at a classification of "moderate"; Germany scored it "slightly irritating".

For the sensitization studies (references 14, NL, AUS, CND, D, US and especially 15, NL, AUS, D) the Netherlands uses only the classifications "positive" and "negative", while Australia and Germany make a differentiation for concentrations. For reference 14 all countries but Australia scored "positive", Australia scored "moderate".

Subchronic toxicity

In the one-year feeding study with dogs (reference 17, AUS, CND, D, US) Australia, Canada and Germany choose a NOEL, while the US did not. The US suggest that the highest dose tested could be either a NOEL or a LOEL, and they are waiting for additional data. Australia and Germany choose 7.9 mg/kg b.w. as the NOEL and Canada choose 6. This difference is due to a conversion factor. The other one-year dog study (reference 18, AUS, D, US) was a strangely performed study. Dose levels were escalated during the study in steps. A clear NOEL can not be given, therefore the countries choose other NOELs or a range.

Developmental and reproduction toxicity

In the 3-generation reproduction study (reference 19, NL, AUS, CND, D, US) Canada chose a lower NOEL than all other evaluating countries, 4 mg/kg b.w. compared to 18.8 mg/kg b.w. The lower NOEL is based on a lower relative thyroid weight in females in the F_2 and an increased relative kidney weight in the F_2 females and in F_{3b} pups. The other countries concluded that this effect was not significant.

In the teratogenicity (reference 20, NL, CND) the Netherlands established a NOEL at 33.3 mg/kg b.w., the lowest dose tested, because the incidence in malformations was not dose related, while Canada concluded that a NOEL could not be established since the incidence of major and minor malformations was high in all dose groups. In the teratogenicity study with rabbits (ref 23, NL, AUS, D, US) the US and Australia established a different NOEL for maternal and embryotoxicity, and the US chose for both endpoints a higher NOEL, 300 and 600 mg/kg b.w. for maternal and embryotoxicity, while Australia established 150 and 300 mg/kg b.w., respectively. The Netherlands and Germany established one overall NOEL, 300 mg/kg b.w. We asked Australia why they chose this lower NOEL on maternal toxicity. The NOEL of 150 mg/kg was based on the reductions in body weight gain and food consumption at 300 mg/kg. Although these effects were not statistically significant, they were considered to be treatment related. Similarly, the reduction in foetal weight at 600 mg/kg, while not significant, was considered treatment related, resulting in a NOEL for embryotoxicity of 300 mg/kg. The US chose the highest NOEL for embryotoxicity, 600 mg/kg b.w., the highest dose tested, because no clear effects were found on the fetuses.

Chronic toxicity

In the two-year toxicology study with mice (reference 26, AUS, US) Australia chose a lower NOEL than the US, 200 versus 1000 mg/kg feed, based on the increase in liver weights at 1000 and 5000 mg/kg feed. The US established their NOEL based on a decrease in body weight gain in females at 5000 mg/kg b.w.

In the 2-year study with rats (reference 27, NL, CND, D) Germany chose a lower NOEL than Canada and the Netherlands. This was based on some decrease in organ weights and an increase in thyroid cell adenomas in the mid dose group. Canada and the Netherlands judged the changes in organ weights as not relevant, because these effects were seen only during the one year observation. The increase in adenomas they established as not dose related.

3.2 Ecotoxicology

For the ecotoxicology and the environmental fate data no clear differences can be found between the various countries. There appeared to be a problem in evaluating the countries' reviews because these data are less comprehensively reported by the various countries than the mammalian toxicology data.

Soil degradation

The Netherlands have a lot of studies available. The Netherlands concluded that the DT_{50} value of pyridate in uncultivated and cultivated soil (reference 29, NL, D) was approximately 5 days. They claimed that this was also the study authors' conclusion. Germany concluded that the DT_{50} value was about 1 day, but Germany provides no further details, so it is difficult to recover why they chose 1 day. We asked Germany and they said that they had problems in interpretation of DT_{50} values of pyridate in field studies because there was no determination of the recoveries. They assumed a fast degradation in soil based on the hydrolysis study.

For reference 32 (NL, AUS, D, US) the countries' evaluations differ. The Netherlands mentioned a DT_{50} of 35 or 40 days, depending on pH, while Australia and the US gave a range of days, 10-60 and 10-30, respectively. Germany gave only a result for DT_{90}, which is similar to that of the Netherlands. Australia and the US gave only a result for the DT_{50}.

Soil, sorption and mobility

For the mobility in soil (reference 34, AUS, CND) it is remarkable that Australia reported only one value (% radioactivity), while Canada reported 4 values (two metabolites in aged and leached soil). Again because, no details are available, it is difficult to clarify this difference.

Birds: acute, subacute and reproduction

All concerned countries evaluated references 36-42 and 44 similarly. Canada is the only country which reported no values, but a conclusion on hazard.

In a reproduction study with ducks (reference 43, NL, AUS, D, US) Australia mentioned a higher NOEC value than the Netherlands, Germany and the US. The Netherlands concluded that at a higher dose a slight effect on number of hatchlings was observed, therefore they chose a lower NOEC. Most countries related the effect concentrations to the nominal concentrations; only the Netherlands stated the actual measured concentrations.

Water organisms: acute and subacute

All concerned countries evaluated the references 45-52 similarly. There are no differences to discuss.

Bioaccumulation

For bioaccumulation in whole fish (ref 54, NL, AUS, D, US) Germany calculated a BCF of 116. The other countries concluded that the BCF was 464.

Insects: acute

There are no differences to discuss.

Earthworms: acute

There are no differences to discuss.

Algae: growth inhibition

There are no differences to discuss.

4 Comparison of the overall hazard characterization

Appendix 4 gives an overview of the general conclusion about the pyridate's hazard in particular study areas. For the most part, countries use a classification system for the study parameter of concern. A favourable feature of hazard and/or risk classifications is the common understanding of the terminology not only among toxicologists but also by the general public. By contrast, a value can only be interpreted by an expert. As can be seen from Appendix 4 the use of classifications is far from complete and because the classifications are not harmonized they vary from country to country. In general it can be concluded that the resulting indication does not differ very much.

Countries' classification of pyridate's acute toxicity ranges from "slight" to "moderate" by the Netherlands, to "low" by Australia, Canada, and Germany. Because acute toxicity is the only study type for which an internationally accepted classification system exists this result seems a little odd. There is also no clear reason for the variation in the classification for sensitization which ranged from "not" to "highly" sensitive.

In the environmental area, only small differences are observed. The only significant difference is the classification of the leaching potential of the main metabolite. According to the Netherlands, Canada, Australia, and the US, the metabolite is to be classified as a leacher. Only Germany states "no tendency" to leach for this metabolite.

There is a large variety in the information used to predict worker exposure. Each country has its own approach. Therefore, more standardization in this area would be useful.

The Netherlands examines respiratory uptake, dermal uptake and systemic health effects, while Australia looks at irritation and sensitization. Canada considers the exposure of a Canadian farmer wearing a cotton overall and no gloves. In Germany, no classification or labelling with respect to workers is considered necessary. Finally, the US does not indicate worker exposure. In Appendix 6, a proposal is given that could serve as a starting point in the discussion about standardizing the approach to assessing worker exposure.

5 Potential for use of reviews by other countries in lieu of conducting separate reviews

Australia

The Australian review on mammalian toxicology is very well ordered. The review explains how each study was performed. The acute toxicity studies are given in a table. Because the table gives enough information, this should be acceptable. The results of other studies are given in a logical way with mention of dose relations and significances. Tables are used when necessary and a useful summary is provided. Our only recommendation is that a reference to the used method would sometimes be helpful.

The Australian review on environmental effects is also well structured. The review tells clearly how studies were performed, and it provides their results in summary form. The only remark we could make is that there are no references made to the original study reports. The summary given is useful.

Canada

The Canadian review on mammalian toxicology is also very well ordered. It explains how each study was performed and describes some in detail (e.g. acute toxicity studies). The study results are also described in detail with tables, when necessary for clarification. It would be helpful to give dose relations and significances more often (for instance reference 21, body weights). Another recommendation is that a reference to the method used could be helpful sometimes. The summary (decision document) is clearly written for the Canadian situation, but clear enough for use by others.

The Canadian review on environmental assessment is not very clear for outsiders, because the different parts were made by different departments. The summary reviews are very helpful to find studies quickly. In these summary reviews no references were given to the original study reports. It could be helpful when in the review all studies are described apart with clear mention of methodology.

Germany

The German review on mammalian toxicology is not very well ordered. For the description of the studies there is no uniform lay out. Some study descriptions are very long, see for instance the 90-day rat oral subchronic toxicity study. The results of the studies are sometimes difficult to find between all the mentioned effects which were not significant or dose related, or effects only seen during the start of experiment, see for instance the 3 months toxicity study in dogs, ophthalmoscopic examinations. For all studies counts that there are

no references given for the method used. It is also not always known for what parameters observations were made; there are no headings 'observations' or 'methods'. Furthermore, not all studies provided by the registrant are reviewed, see for instance ref A13 and A14 at the acute toxicity. The summary is clear.

The German review on environmental assessment is too short. The studies are not described individually. It is not known according to what methods the studies are performed. There are no clear study descriptions given. There are also no references given to the original studies. There is also no summary.

US

The reviews prepared by the United States are not useful to us. All studies are described individually, but in a very extensive way. A system cannot be found in the pack of paper. Furthermore, for the mammalian toxicology there is no summary available, only a very short review with NOEL's. The summary of the environmental data is more useful. In addition, the US prepare a Decision Memorandum, in which the main conclusions of the findings are given. This document takes care for the necessary integration of decisions on the several study areas.

The Netherlands

The reviews are well ordered with headings. All reviews give a description of the method or a reference to a method. Missing information is stated. The results are given with mention of dose relations and/or significances. Sometimes tables are used to clarify the results. All reviews are accompanied with a reference to the original study. When necessary remarks are made on the performance of the study. There are separate summaries for the mammalian toxicology, resulting in an ADI, and for ecotoxicology, in which the fate of the substance is described.

5.1 Use of reviews

Other reviews can be used by other countries when the review is based on a full study report. The review should contain a clear description about the method used (in the attached Appendix 5 is given what parameters should be described) or a reference to the method used (OECD, EC, BBA, FDA). The results should be described clearly with mention of significances and dose relations (see also Appendix 5). A clear reference to the described study is also necessary.

5.2 Final outcome/overall hazard assessment

- Toxicology

Netherlands:	ADI: 0.18 mg/kg b.w./day
Australia:	ADI: 0.2 mg/kg b.w./day
Canada:	ADI: 0.04 mg/kg b.w./day for pyridate and CL9673 0.03 mg/kg b.w./day for pyridate alone
Germany:	ADI: 0.03 mg/kg bw/day guideline for drinking water (BGA, 1993): 105 µg/l
US:	Reference Dose (RfD): 0.11 mg/kg b.w./day.

- Ecotoxicology

For hazard assessment see Appendix 4

5.3 Legal issues

With respect to legal issues the following has to be remarked. In some countries there are legal restrictions against making the information on the characteristics of pesticides, physico-chemical, toxicological, and ecotoxicological, known to the general public. Looking at pyridate for instance, Germany had to ask for special permission to pass the information to other OECD countries, and Switzerland was not able to cooperate at all. Only the Swiss government's decision on the use of the substance was made available. In the Netherlands it is not allowed to publish the information about the composition of the formulation.

In general, the test reports on the research carried out with the substance are claimed confidential by the companies, while the final evaluation by the government is more often open to the general public.

6 Recommendations

1. Appendix 5 gives an overview of the items that should be available in the country's summary and evaluation if this is to be accepted by the Netherlands. The items are listed per study subject.

2. The units in the summary and the evaluation have to be converted to standardized units using the SI-system. It is very difficult to compare data given in different units. Also the internal consistency of the data is improved.

3. Standardized classifications for most items are very helpful in interpreting the data. There is very little done on the international level to strive for harmonizing classifications. In Appendix 6 an overview is given of the Dutch classifications used for several subjects. An international discussion on this matter is necessary.

4. A standardized format of the evaluation of studies makes a comparison of the evaluative reports of different countries a much more easy job. Essential information should be highlighted, so a colleague of another country can establish quickly all the essential information.

5. Missing information in a study report should be clearly indicated. A competent authority can identify easily how relevant this missing information will be for his own country.

6. Remarks on the performance of the study, deviations from a given protocol, etc. should be indicated clearly.

7. GLP-requirements should be met for the studies performed as far as relevant.

8. Expert opinion and a discussion between a company and a governmental expert may solve several problems arising during the evaluation process. The result of this bilateral consultation should be clearly reported.

Appendices

Appendix 1. Types of Data Reviews

Types of review		NL	AUS	CND	D	US	CH
1.	Coverage of data reviews						
	level 1: individual studies	X	X (tox)	X (tox)		X (tox)	
	level 2: study categories		X (ecotox)	X (ecotox)	X (tox)		
	level 3: test areas				X (ecotox)	X (ecotox)	
	level 4: all data on pesticide						
	other (describe)						no evaluation available
2.	Length of data reviews (tox and ecotox)						
	1-10 pages						
	11-30 pages						
	31-50 pages						
	51-100 pages		X		X		
	101 or more pages	X		X		X	
3.	Language of reviews	English	English	English	English	English	
4.	Reviews contain a summary (write yes or no)	yes	yes	yes	yes (tox part only)	yes (tox) (per study)	

Types of review		NL	AUS	CND	D	US	CH
5.	Language of summaries (write in)	Dutch (for pilot project translated)	English	English and French	English	English	
6.	Reviews document conduct and findings of study (write yes or no)	yes	yes	yes	no/yes	yes (tox)	
7.	Reviews include conclusions of reviewer about inherent toxicity (hazard characterisation levels) (write yes or no)	yes	yes	yes	yes	no (tox) yes (ecotox)	
8a.	Information on the quality of the data (write yes or no)	yes	no	no	no	yes (tox)	
8b.	What criteria were followed	OECD, EPA, BBA				unknown	
8c.	When not according to criteria are studies judged acceptable and included in the review	yes				unknown	

Appendix 2. REFERENCES

1. ST-9551-Acute toxicity to mice and rats; 4-weeks-range-finding-test in rats and dogs (summary). Unpublished report of Chemie Linz AG, DFP/We/Wh - UL/1806, February 1977.

2. Ullmann, L. (1987). Acute oral toxicity study with pyridate technical in mice. Project no. 088323, RCC, Switzerland.

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Appendix 3. Comparison of Results in Countries' Data Reviews

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
	Acute oral toxicity							
1	oral mouse	LD_{50} (mg/kg bw)	> 10000	-	m: 11550 f: 28400	> 10000	-	-
2	oral mouse	LD_{50} (mg/kg bw)	-	> 10000	-	> 10000	-	-
3	oral rat	LD_{50} (mg/kg bw)	-	m: 5993 f: 3544	-	m: 5993 f: 3544	-	-
4	oral mouse, CL 9673	LD_{50} (mg/kg bw)	518.7	-	*	-	-	-
5	oral mouse, CL11344 WP oral rat, CL11344 WP	LD_{50} (mg/kg bw) LD_{50} (mg/kg bw)	> 7500 m: 1113 f: 311-1947	-	-	-	> 7500 m: 1.69 ml/kg f: 2.28 ml/kg	-
6	dermal rabbit	LD_{50} (mg/kg bw)	-	> 2000	> 2000	> 2000	-	-
7	dermal rabbit	LD_{50} (mg/kg bw)	> 3450	-	> 2000	> 2000	-	-
8	inhalation rat	LC_{50} (mg/m^3)		4370	4400	4370	-	-
9	inhalation rat, CL 11344/69 WP	LC_{50} (mg/m^3)	> 2140	-	> 2140	-	-	-
10	eye irritation		irritating	moderate	mild	not irritating	not irritating	-
11	eye irritation, Lentagran WP		irritating	-	mild	-	*	-
12	skin irritation		moderate	moderate	moderate	slight-moderate	moderate	-
13	skin irritation, Lentagran WP		not irritating	-	not irritating	-	*	-
14	sensitization		positive	moderate	positive	positive	positive	-
15	sensitization		positive	negative up to 3% positive ≥10%	-	negative up to 3% positive ≥10%		-

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
16	sensitization, Lentagran WP		positive	-	positive	-	*	-
	Subchronic toxicity							
17	1 year feeding dog	NOEL (mg/kg bw)	-	7.9	6	7.9	NOEL not-determined	-
18	1 year oral dog	NOEL (mg/kg bw)	-	30	-	5-30	20	-
	Developmental and reproductive toxicity							
19	3 generation reprod. rat	NOEL (mg/kg bw)	18.8[1]	18.8[1]	4[1]	18.8[1]	18.8[1]	-
20	teratology rat	NOEL (mg/kg bw)	100[6] and 33.3[7]	-	a new study is required	*	-	-
21	teratology rat	NOEL (mg/kg bw)	165	165	165	165	165	-
22	teratology rabbit	NOEL (mg/kg bw)	*	-	30[1]	*	-	-
23	teratology rabbit	NOEL (mg/kg bw)	300[1]	150[6] and 300[7]	-	300[1]	** 300[6] and 600[7]	-
24	teratology rabbit	NOEL (mg/kg bw)	-	> 90 [1]	90 [1]	*	-	-
	Chronic toxicity							
25	carc. oral mouse	NOEL (mg/kg bw)	-	-	not carc., 28.6	not carc., 24	-	-
26	carc. feeding mouse	NOEL (mg/kg fd)	-	not carc., 200	-	-	oncogenic NOEL > 5000 systemic NOEL 1000	-
27	2 yr feeding rat	NOEL (mg/kg bw)	18	-	20	3.5	-	-
28	carc. rat	carcinogenicity	no	-	no	no	-	-

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
	Soil degradation							
29	field conditions	DT_{50} (days)	ca. 5[9]	-	-	about 1	-	-
30	aerobe, 3 standard soils	DT_{50} (days) DT_{90} (days)	< 6 13-27	-	-	*	-	-
31	clay loam, ^{14}C-pyridate clay loam, CL-9673	DT_{50} (days) DT_{90} (days) DT_{50} (days) DT_{90} (days)	< 0.04 < 1 < 14 < 45	-	-	*	-	-
32	aerobe, 4 soils, CL-9673	DT_{50} (days) DT_{90}2,3 (days)	35[2] 40[3] > 70	10-60	27-30	DT_{90} > 70	10-30 [4]	-
	Soil: sorption and mobility							
33	Leaching behaviour	% leach	in 5 different studies with 3 different soils 0.3-28% leach	-	0.2-28	due to its instability the leaching potential is negligible	-	-
34	Mobility in soil of aged ^{14}C-pyridate in 4 different soils (pH5, %om2; pH5.9, %om3.1; pH6.6, % om0.7; pH7.4, %om2.3)	% leach	-	3.0[11] 20.1[11] 55.1[11] 64.9[11]	63.7, 41.8, 7.3, 4.4[10] 3[11], 22.7, 11.9 15[10] 70, 15.7, 3, 1.7[10] 58.7, 8.7, 4.2, 4[10]	-	-	-

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
35	Leach (%) of ^{14}C-pyridate in 4 diff. soils pH6.7, 3.1%om pH6.8, 1.6%om pH6.7, 2.9%om pH6.5, 0.5%om	 % leach % leach % leach % leach	-	 52.39 35.65 6.67 2.15	-	-	-	-
	Birds: acute, subacute and reproduction							
36	Phasianus sp.	LD_{50} (mg/kg bw)	> 10000	> 10000	low	> 10000	-	-
37	Colinus virginianus	LD_{50} (mg/kg bw)	1505	1505	low	1505	-	-
38	Anas platyrhynchos	LD_{50} (mg/kg bw)	> 10000	> 10000	low	> 10000	-	-
39	Japanese quail	LC_{50} (mg/kg fd)	> 10000	*	low	> 10000	-	-
40	Colinus virginianus	LD_{50} (mg/kg bw)	1269	1269	-	1269	1269	-
41	Anas platyrhynchos	LC_{50} (mg/kg fd)	> 5000	> 5000	low	> 5000	> 5000	-
42	Colinus virginianus	LC_{50} (mg/kg fd)	> 5000	> 5000	low	> 5000	> 5000	-
43	Anas platyrhynchos, reprod.	NOEC (mg/kg fd)	595[5]	900	-	640	640	-
44	Colinus virginianus, reprod.	NOEC (mg/kg fd)	1484[5]	1600	-	1600	1600	-
	Waterorganisms: acute and subacute							
45	Daphnia magna	LC_{50} (mg/l), 48 h	1.08	-	-	-	1.08	-
46	Daphnia magna, CL 9673	LC_{50} (mg/l), 24 h LC_{50} (mg/l), 48 h	> 30 > 26	- 26	- 26.2	-	26.14[15]	-
47	Mysid sp., LX101-01-45 WP	LC_{50} (mg/l), 96 h	*	2.9-4.8	2.9-4.8	-	3.8 (3.3-4.4)	-
48	Cyprinus carpio Ictalurus melas Lepomis macrochirus Leuciscus idus forma Salmo gairdnerii	LC_{50} (mg/l), 96 h LC_{50} (mg/l), 96 h LC_{50} (mg/l), 96 h LC_{50} (mg/l), 96 h LC_{50} (mg/l), 96 h	> 100 48 > 100 > 100 81	> 100 48 > 100 > 100 81	> 100 48 > 100 > 100 81	-	-	-

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
49	Salmo gairdnerii	LC_{50} (mg/l), 96 h	-	> 2 (40% mortal.)	-	-	> 1.2	-
50	Lepomis macrochirus	LC_{50} (mg/l), 96 h	-	> 2	-	-	> 2.1	-
51	Cyprinus carpio, CL 9673	LC_{50} (mg/l), 96 h	-	61.1	-	61.1 (EC_{50})	-	-
52	Salmo gairdnerii, CL 9673	NOEC (mg/l), 21 d	-	≥20	-	20	-	-
	Bioaccumulation							
53	BCF, Chlorella fusca		7328-0.1 at 3.5-47 h.	-	inconsistent results	-	*	-
54	BCF, Lepomis macrochirus, whole fish		464	464	464	116	464	
55	BCF^{14}, Ictalurus sp		1.98	< 3	< 3	-	-	-
56	BCF, Chlorella fusca, CL9673		*	no tendency for bioaccumulation	-	-	-	-
57	BCF, CL9673, Chlorella sp		40 h, 0.14	no tendency	*	-	-	-
	Insects: acute							
58	Apis mellifera	LD_{50} (µg/bee), oral idem, contact idem, spray	> 100 > 160 > 250	-	> 100 > 160	-	-	-
59	Apis mellifera	LD_{50} (µg/bee)	> 100	> 100	-	> 100	> 100	-
	Earthworms: acute							
60	earthworms	LC_{50} (mg/kg), 7d LC_{50} (mg/kg), 14 d	> 1000 799	- > 799	-	> 1000 799	-	-

Ref	Study type	Endpoint	NL	AUS	CND	D	US	CH
	Algae: growth inhibition							
61	Scenedesmus subspicatus	EC_{50} (mg/l), 96 h NOEC (mg/l), 96 h	82 48	82	82	82		
62	Scenedesmus capricornu-, tum, CL9673	EC_{50} (mg/l), 96 h LOEC (mg/l), 96 h NOEC (mg/l), 96 h	-	4.93 3.09 1.70				

* Value not to be found or used in summary

[1] NOEL for maternal and embryo toxicity
[2] At pH 7.2-7.5
[3] At pH 5.4-5.8
[4] In the reference labelled CL-9673, in the summary unlabelled CL-9673
[5] Actual concentrations
[6] Maternal toxicity
[7] Embryo toxicity
[9] Value according to the author. Due to the few sampling dates exact calculation is not allowed
[10] The order is amount (%) of CL9673 recovered from aged soil and leached soil followed by amount (%) CL 9673-O-CH recovered from aged and leached soil columns
[11] The amount of 'label' appearing in the leachate (% radioactivity)
[12] Recovery
[13] At this conditions the results were not given
[14] Accumulation of aged soil residues
[15] The exposure time is not given

Appendix 4. General Conclusions About Pyridate's Hazard in Particular Study Areas

Study type	NL	AUS	CND	D	US
human					
acute toxicity	slight to moderate	low	low	low	-
skin irritation	moderate	moderate	-	slight to moderate	-
eye irritation	irritating	slight	-	-	-
sensitization	positive	moderate to high	not	slight	-
reproduction	no effect	no effect	no effect	no effect	-
teratogenicity	no irreversible structural effects	no teratogenicity	no teratogenicity	no teratogenicity	-
genotoxicity	not	not	not	not	-
carcinogenicity	not	not	not	not	-
environment					
solubility	slightly	low	low	-	-
idem CL9673	moderately	high	-	-	-
volatility	very slightly	low	-	-	-
degradation in soil	readily	-	-	rapidly	rapidly
idem CL9673	fairly	fast	-	-	-
mobility	slightly mobile to immobile	-	-	-	-
idem CL9673	slightly mobile to mobile	highly	-	-	-
leaching	-	-	low probability	no tendency	-
idem CL9673	intermediate risk	leacher	potential	no tendency	readily
birds	slightly toxic	slightly to non-toxic	low toxicity	no tendency	slightly to non toxic

Study type	NL	AUS	CND	D	US
algae	slightly toxic	slightly toxic	no effect	low toxic	-
idem CL9673	-	moderately	-	-	-
Daphnia	moderately toxic	non-toxic	-	toxic	moderately toxic
idem CL9673	-	slightly toxic	slightly	-	-
shrimps	-	-	moderately toxic	-	moderately toxic
clam embryos	-	-	extremely toxic	-	-
fish	very slightly	moderately to non-toxic	marginally toxic	low	not more than moderately toxic
idem CL9673	-	slightly	marginally toxic	-	-
estuarine fish	-	-	-	-	not more than highly toxic
bees	slightly toxic	non-toxic	-	not dangerous	non toxic
earthworms	-	non-toxic	low	very low toxic	
workers					
respiratory uptake	not expected				
dermal uptake	not expected				
systemic health effects	not expected				
irritant and/or sensitizing effect		not expected			
Canadian farmer wearing cotton overall and no gloves, spraying at a rate of 1.35 kg ai/ha and treating 48 ha/day			MOS = 6[1]		
classification and labelling				not necessary	

[1] MOS: margin of safety = NOEL : exposure

Appendix 5

All parameters of the respective studies should be described in the data review before the Netherlands can use other reviews. The parameters considered to be essential by the Netherlands are listed below:

For all studies

- chemical identification of the test substance
- purity
- reference

Acute toxicity

- species
- route
- duration (in case of inhalation)
- result

Subchronic toxicity

- species
- number/sex group
- route of administration
- dose levels
- solvent
- duration
- observations
- results per sex/group

Developmental and reproductive toxicity

Reproduction
- species
- number of offsprings per generation
- number/sex per group
- route of administration
- dose levels
- solvent
- time of administration
- observations of parental animals
- observations per litter
- observations of pups
- results per generation and per sex

Teratology
- species
- number per group
- exposure time
- route of administration
- observations of dams, pregnancy and litter
- observations of fetuses
- results of dams and fetuses

Chronic toxicity

- species and strain
- number/sex/group
- dose levels
- route of administration
- duration of the study
- observations (also for carcinogenicity ?)
- results per sex and per group

Soil metabolism

- soil type
- soil characteristics (temperature, percentage organic material, pH, n pF-value, CEC)
- result (DT_{50})

Mobility

- soil type
- soil characteristics (pH, CEC, percentage organic material)
- in case of aging the days
- column length
- water layer
- leaching profile in soil or 50% leaching depth

Avian testing

- species
- route
- exposure time
- recovery period
- result

Aquatic testing

- species
- type of experiment (static, semi-static, continuous flow)
- age/length, medium (pH, O_2, temp, hardness)
- exposure time
- result
- nominal/measured concentration

Bioaccumulation

- species
- type of experiment (static, semi-static, continuous flow)
- age, length
- medium
- exposure time
- results (whole organism, wet/dry weight)
- nominal/measured concentration

Appendix 6. Classifications

Acute toxicity

LD_{50} oral mg/kg	LD_{50} dermal mg/kg	LC_{50} inhalation $mg/m^3/4hr$	description acute toxicity	EC-classification
≤25	≤500	≤500	very toxic	very toxic
25-200	50-400	500-2,000	toxic	toxic
200-2,000	400-2,000	2,000-20,000	moderately toxic	harmful
> 2,000	> 2,000	> 20,000	slightly toxic	

Skin irritation

score according to Draize:

≤0.5	not irritating
0.5-2	slightly irritating
2-5	moderately irritating
5-8	severe irritating

Eye irritation

score according to Draize:

0 - 5	not irritating
5 - 15	slightly irritating
15 - 30	irritating
30 - 60	strongly irritating
60 - 80	severely irritating
80 - 110	extremely irritating

Physical properties

* Solubility (S) at 20-25 °C:

	S (mg/l)
- very slightly soluble	< 0.1
- slightly soluble	0.1 - 10
- moderately soluble	10 - 1000
- readily soluble	≥ 1000

* Volatility (P) at 20-25 °C:

	P (Pa)
- very slightly volatile	< 0.0001
- slightly volatile	0.0001 - 0.01
- moderately volatile	0.01 - 1
- volatile	1 - 100
- highly volatile	≥ 100

Degradation and mobility

* DT_{50} at 20 °C:

	DT_{50} (d)
- very slightly degradable	> 180
- sightly degradable	60 - 180
- fairly degradable	20 - 60
- readily degradable	< 20

* Mobility at 20 °C.

	Rf	Ks/l (dm^3/kg)	K_{om} (dm^3/kg)
- immobile	0-0.09	> 2.6	> 100
- slightly mobile	0.10-0.34	0.53-2.6	20-100
- moderately mobile	0.35-0.64	0.15-0.53	5-20
- mobile	0.65-0.89	0.03-0.15	1-5
- highly mobile	0.90-1.00	< 0.03	< 1

Toxicity

* Waterorganisms, acute:
algae (96-h EC_{50}), Daphnia (48-h LC_{50}) and fish (96-h LC_{50}).

RIVM/ACT-classification	EC-classification	E(L)C_{50} (mg/l)
- very slightly toxic	no EC classification	> 100
- slightly toxic	harmful	10 - 100
- moderately toxic	toxic	1 - 10
- highly toxic	very toxic	< 1

* Waterorganisms, chronic

	NOEC (mg/l)
- very slightly toxic	> 1
- slightly toxic	0.1 - 1
- moderately toxic	0.01 - 0.1
- highly toxic	< 0.01

* Birds, acute oral

	LD_{50} (mg/kg bw)
- slightly toxic	> 500
- moderately toxic	50 - 500
- toxic	5 - 50
- highly toxic	< 5

* Earthworms

	LC_{50} (mg/kg dry soil)
- very slightly toxic	> 1000
- slightly toxic	100 - 1000
- moderately toxic	10 - 100
- toxic	1 - 10
- highly toxic	< 1

* Bees, contact en oral

	LD_{50} (µg/bij)
- very slightly toxic	> 100
- slightly toxic	10 - 100
- moderately toxic	1 - 10
- toxic	0.1 - 1
- highly toxic	< 0.1

Bioaccumulation

	BCF
- slightly accumulating	< 100
- moderately accumulating	100 - 1000
- highly accumulating	> 1000

ANNEX 8

OVERVIEW OF THE PESTICIDE DATA REVIEW PROCESS IN PILOT PROJECT COUNTRIES AND ORGANISATIONS

OECD Secretariat

Contents

1. Introduction

This report describes basic elements of the data review and re-registration processes in the countries and organisations participating in the Pilot Project. Its purpose is to provide an overview of the process by which pesticides are evaluated and review documents developed. The report considers, for example, the history and general characteristics of the countries' pesticide re-registration programmes; the number of staff involved in data review and the extent to which they work independently or in teams; the use of guidance documents, peer reviews or other measures to ensure consistency of data reviews done by different staff members; and the measures taken to ensure that both the review documents and the studies included in them are of high quality. A general comparison of the Pilot Project participants' approaches is given below, followed by a summary table that highlights key points. The report then describes in more detail the data review and re-registration processes in the various countries and organisations participating in the Pilot Project.

2. Comparison of Pilot Project participants' approaches

2.1 Re-registration

Pesticide re-registration is an activity that exists in two principal forms among the countries and organisations participating in the Pilot Project. Nearly all of the countries are involved in re-registration as a means to update and critically re-evaluate the databases of "old" pesticides, i.e. those registered before the mid-1980s. Several countries also use re-registration as a "housekeeping" exercise to revisit all pesticide registrations on a regular basis -- every 5 years, for example -- with a less comprehensive review of the supporting data. Most of the Pilot Project participants' re-registration programmes are "formal" in the sense that they have established deadlines and priorities for reviewing all relevant chemicals. Some countries, however, have instituted their programmes on more of an ad-hoc basis, re-examining chemicals in response to new risk findings, action taken by another country, or some other factor. Perhaps the greatest differences are in the size and time-scale of the re-registration programmes in different Pilot Project countries. For some countries, the re-registration of one chemical is anticipated to take as long as 15 years (numerous chemicals would undergo re-registration simultaneously, but the programme would nevertheless extend well into the 21st century). In other countries, the entire re-registration programme for all old active ingredients has been given less than 10 years.

2.2 Data review

Not surprisingly, the Pilot Project participants also have many differences in their data review processes. Significant differences are found in: the number of staff who are involved directly in conducting data reviews and writing review reports, the extent to which these staff

work independently or with others, the extent to which data review and pesticide re-registration are concentrated in one ministry or co-ordinated among several, and the extent to which the data review reports are peer reviewed by government or outside experts. To a considerable extent, these differences may be the result of differences in the regulatory ministries' size and resources (especially number of staff) and structure. Other factors are undoubtedly important as well -- e.g. the degree to which decision makers are able to trust the work of one or a few scientists working independently, rather than relying upon multiple layers of peer-review.

One very important factor -- especially since it suggests a common ground for future co-operation -- is that the participants appear to have much in common in their approach to ensuring data quality, applying hazard criteria, and ensuring the comprehensiveness of their reviews. For example, most participants say they prefer that studies comply with principles of good laboratory practice (GLP) but that this is not an absolute requirement, given the fact that old studies may not comply but may still be valid or useful. The solution for most participants is to review non-GLP studies on a case-by-case basis and, if found valid, to include them as supporting data in a pesticide data review. Similarly, nearly all participants say they prefer studies to be done following OECD test guidelines (many countries are open to accepting studies done by other guidelines and some prefer or require use of their own national test guidelines) although this "requirement" is applied with flexibility, since OECD guidelines have not been written for all studies. In the same vein, most participants do not apply hazard criteria as absolute triggers for non-approval of a pesticide, but use them (if they exist) as guidelines, to be applied with scientific judgement. Essentially all of the participants regard pesticide re-registration as a very inclusive and comprehensive effort, with the result that all take into account the full body of available data -- old and new studies and other available information -- in conducting their re-registration reviews. Nearly all the participants require the full data reports rather than relying on summaries, although summaries are sometimes used for specific purposes.

2.3 Report Availability

Countries have different policies regarding the confidentiality or availability of their pesticide data review reports. Six of the countries participating in the Pilot Project, as well as the Joint FAO/WHO Meeting on Pesticide Residues, indicate that their full reports are available to other countries. Three of the countries and the JMPR also make the full reports available to the public. Other project participants can distribute only summaries of their reports or, in some cases, the final regulatory decision. (For purposes of the Pilot Project, several countries with restrictions on report distribution obtained special approval to provide full data review reports to other government authorities.) Such policies restricting report distribution would clearly present a barrier to international co-operation in pesticide review and re-registration. However, there are signs of a trend toward greater openness, influenced no doubt by the European Community Directive 91/414 which will require European countries to share their review reports. A number of the Pilot Project participants who have policies restricting report distribution indicate that their policies will soon change as a result of the EC Directive or national legislation.

2.4 Summary Table

DATA REVIEW PROCEDURES		AUS	CAN	DEN	FIN	GER	NL	NZ	NOR	SWE	SWI	UK	USA	JMPR
BACKGROUND ON RE-REGISTRATION PROGRAMME														
re-registration programme is	formal, with set priorities and deadlines	√	√	√	√	√	√		√	√		√	√	√
	ad hoc							√			√			
re-registration includes	re-evaluation of old pesticides - extensive re-review of data	√	√	√	√	√	√	√		√	√	√	√	√
	periodic renewal of all pesticide registrations - less extensive data review		√	√	√				√	√				
date (year) re-registration programme began		1994	1960s	1987	1969		1988		1963			1986	1988	1963
registration period before re-evaluation required (in years)			5	8	8	max 10			5	5				
DATA REVIEW STAFF AND PROCESS														
number of staff who evaluate data and prepare review documents for	toxicology, residue data	4(11)[1]	7	2	4	11[1]	6	2	2	3		17[2]	59	8-10
	environmental/ecotoxicology data	2(4)	7	3	4	13[1]	3	1	1	9		7[2]	41	
	occupational health and safety	1(3)			1	11								
	use/efficacy	3	1	2	3	6		2	1-2			19[2]	12	6-8
	all areas	10	15	7	12	44-50	9	5	3	12		43[2]		
data reviews are based primarily on	summaries							√			√			
	full study reports	√	√	√	√	√	√		√	√		√	√	√

DATA REVIEW PROCEDURES		AUS	CAN	DEN	FIN	GER	NL	NZ	NOR	SWE	SWI	UK	USA	JMPR
in the absence of new studies, old studies are	included and re-evaluated critically	√	√	√		√	√	√	√		√	√	√	√
	included with only a brief re-review (old assessment is used)		√		√					√				
in conducting their evaluations, reviewers	generally work independently	√	√	√	√	√	√	√	√	√		√	√	√
	work as part of a team			√			√	√		√	√		√	√
	obtain comments from colleagues on draft evaluation documents, either through meetings or by distributing copies for review	√	√	√	√	√	√	√		√		√	√	√
	consult with other reviewers, senior staff or outside experts in specific fields	√	√		√	√	√	√	√	√				
QUALITY CONTROL														
data review documents undergo peer review		√	√		√	√	√		√	√	√	√[2]	√	
country has guidelines or procedures to guide reviewers in evaluating/interpreting studies			√	√		√	√			√		√[2]	√	
hazard levels/triggers are	applied strictly						√							
	applied with flexibility			√		√		√		√		√[2]	√	
	no specific levels set	√	√		√				√		√			√
studies are accepted if done according to test guidelines of	OECD	√	√	√	√	√	√	√	√	√	√		√	√
	European Commission	√		√	√	√	√		√	√	√[3]			
	U.S. EPA	√	√	√	√	√			√	√	√[3]		√	
	German BBA	√			√	√			√	√	√[3]			
	other	√		√		√	√							√

DATA REVIEW PROCEDURES		AUS	CAN	DEN	FIN	GER	NL	NZ	NOR	SWE	SWI	UK	USA	JMPR
compliance with GLP is	strictly required													
	required but with flexibility	√	√	√	√	√	√	√		√		√	√	
	not required								√		√			√
laboratories	are monitored for GLP compliance		√	√		√				√	√	√	√	
	may be audited on request	√			√	√	√							
	country does not have a monitoring programme							√	√					√
data reviews indicate compliance with GLP	for each individual study		√	√				√	√				√	
	for the review generally				√[4]		√			√				
	do not indicate GLP compliance	√				√					√	√		√
country has a system for tracking studies reviewed		√	√	√		√	√	√	√	√		√	√	√
AVAILABILITY OF DATA REVIEW REPORTS														
full reports are available	to other countries (natl. authorities)			√	√[5]		√	√		√			√	√
	to the public							√		√			√	√
summaries only are available	to other countries	√	√											
	to the public	√	√				√							
regulatory decisions only are available	to other countries					√[6]					√			
	to the public			√	√	√[6]					√			

[1]numbers in parentheses indicate staffing levels for 1996/97
[2]agricultural pesticides only
[3]if guidelines are internationally accepted
[4]in toxicology reviews only
[5]to other Nordic countries
[6]this approach will change with implementation of EC Directive 91/414

3. Descriptions of Pilot Project participants' re-registration and data review processes

3.1 AUSTRALIA

Background on re-registration programme

Australia began a formal pesticide re-registration programme in 1994 under an Existing Chemicals Review Program run by the National Registration Authority. Previously, the review of "old" pesticides was conducted on an ad-hoc basis. The new programme will carry out a periodic and systematic review of existing agricultural and veterinary chemicals on a priority basis. Re-registration reviews will continue to be undertaken in the same manner as new pesticide reviews, although the re-registration programme itself will likely be kept separate from mainstream registration activities. It will still be possible for any of the participating agencies to conduct *ad hoc* reviews outside the formal review programme as the need arises.

Re-registration priorities will take into account the views of the various government agencies involved in pesticide assessment as well as input from the public who may nominate chemicals for review. Chemicals will be selected on the basis of agreed criteria for health and environmental hazard, exposure potential, age and adequacy of the database, efficacy, international regulatory actions and trade implications. A two-stage process has been proposed: in stage 1 chemicals will be scored against the selection criteria and public nominations will be called for; in stage 2 a priority list of chemicals for review will be developed based on the outcome of stage 1. The Board of Australia's National Registration Authority will determine the priority list and will reassess priorities as chemicals are reviewed.

At the end of the review process, regulatory decisions will be taken with both reviewers and administrators involved. Regulatory decisions will consider the weight of evidence and will be based on such factors as exposure and extent and pattern of use, in addition to hazard. Efficacy will be considered but alternative pest-control methods will not normally be taken into account. Individual studies will not usually be identified as the basis for a regulatory decision; however, in cases where individual studies indicate concern, their importance in the decision would be noted. Draft decision documents will be released for public comment before final decisions are produced by the National Registration Authority.

Data review staff and process

The National Registration Authority for Agricultural and Veterinary Chemicals is responsible for co-ordinating all registration and re-registration activities for agricultural and veterinary chemical products. Re-registration activities are carried out under the Existing Chemicals Review Programme. The National Registration Authority itself assesses chemistry, efficacy and trade issues, while co-ordinating the conduct of health and environmental assessments done by other agencies, as described below.

Under the formal re-registration programme, there are initially a total of ten people involved in evaluating pesticide data and preparing reports. Additional resources will depend upon the degree of financial support allocated to the programme. The majority of the re-registration staff will have had experience in both new product assessment and review of old chemicals under the previous *ad hoc* approach. The various authorities involved in pesticide review may also elect to have some work done by outside experts/consultants.

- Toxicology data are reviewed by the Chemical Safety Unit (CSU) of the Commonwealth Department of Human Services and Health. The re-registration/review activities of the CSU are carried out within the Chemicals Review Section, which is a separate evaluation unit from that which evaluates new chemical applications. The entire toxicology data package for a chemical is reviewed by a single evaluator, who is able to consult regularly with other evaluation staff. Four staff members in the CSU are responsible for evaluating toxicology and residue data.

- Occupational health and safety data are reviewed by Worksafe Australia's Chemical Assessment Branch in a section devoted to the assessment of new and existing pesticides. The branch has one staff member responsible for reviewing occupational data on pesticides.

- Environmental data are evaluated by the Chemical Section of the Commonwealth Environment Protection Agency, which assesses new and existing agricultural, industrial and veterinary chemicals. Two staff members are responsible for pesticide reviews.

- Chemistry, efficacy and trade issues are assessed by three staff members in the National Registration Authority's Existing Chemicals Review Programme.

Under the formal re-registration programme, new staff will be trained on the job under the guidance of experienced reviewers, as was done in the past under the *ad hoc* programme. New staff assessments will be closely monitored and in some cases may be subject to further scrutiny by expert committees outside the government. All staff involved in pesticide review will have the opportunity for further training and professional development. A programme for data evaluation staff to pursue research within academic institutions (1 day/week) is available, along with on-the-job training, seminars, funding for conferences (at least one per year) and departmental development awards.

Quality control

1. Consistency of reviews

While Australia has no formal guidelines for the evaluation and interpretation of toxicology and environmental studies, consistency of reviews is achieved through in-house training of new staff (as described above), peer review by senior evaluators, and use of an internal guide for the structuring and presentation of review documents.

All toxicology evaluations and draft recommendations for public health consideration are peer reviewed first by a senior evaluator (principal toxicologist), and next by the chief toxicologist of the Chemical Review Section. The toxicology evaluation is subsequently

considered by the Scientific Director of the Chemical Safety Unit and/or the Advisory Committee on Pesticides, an expert scientific committee associated with the Chemical Safety Unit. The Advisory Committee on Pesticides gives independent advice to the Chemicals Safety Unit on issues of policy and practice having possible implications for public health and the proper use of existing chemicals in agriculture and elsewhere. Membership on the committee is on the basis of expertise and experience.

Environmental assessments undergo a similar course of peer review, with possible external review by State and Territory environmental representatives.

Occupational health and safety assessments are based on specific required information regarding exposure, and set criteria for evaluation of this information. Risk assessments conducted by Worksafe Australia are based on a review of the product's toxicity (supplied by Department of Human Services and Health), its anticipated conditions of use, and any supplementary information on human health effects.

2. Data quality

Australia requires studies to be undertaken in compliance with international GLP principles, preferably those of OECD, the U.S. or Japan. The requirement is applied with flexibility, however, because most studies are conducted in other countries and often for an international market. Studies not done according to GLP are assessed on their individual scientific merit: their significance in regulatory decision making depends upon the type of study, its importance in the overall assessment, and the confidence that can be placed upon the conduct of the study. Australia's data reviews do not indicate whether or not the studies complied with GLP.

The National Association of Testing Authorities (NATA) has the responsibility for assuring GLP compliance in Australia. Penalties for falsifying data are set at $250,000 for a corporate body, $50,000 for an individual and/or 10 years jail.

Australia accepts any recognised test guidelines for environmental and toxicological data (OECD, U.S. EPA etc), although studies not following such guidelines are also included in data reviews if they are judged to be scientifically valid. Environmental data reviews indicate whether studies followed specific test guidelines; toxicology reviews do not. Because test guidelines are not yet established for defining occupational exposure and risk, all available studies on human exposure, including occupational exposure, are evaluated.

3. Data used/reviewed

Australia makes an effort to cover all available data, but does not necessarily request a new data package for every pesticide re-review. Old studies are included if they are judged to be valid and useful. To the extent possible, a complete data package is obtained before the review begins, and data in all test areas are reviewed simultaneously. Re-registration as well as registration reviews are conducted on the detailed data and not on summaries, although raw data (slides, lab books etc.) are not usually requested. Each agency is allowed the discretion to make use of data reviews done by other countries.

4. Study documentation

Although Australia does not have a system for keeping track of all studies reviewed, a database and tracking system is being developed by the National Registration Authority. In the meantime, all studies within a toxicological data package are logged onto a computerised database according to study type. The Chemical Safety Unit has developed a new database which details toxicological studies reviewed.

Availability of reports

All agencies participating in the review programme have access to Australia's evaluation reports, with due consideration given to the need to protect confidential data. Worksafe Australia use the toxicology report prepared by the Chemical Safety Unit as part of its consideration of the occupational health and safety aspects of the chemical. Full evaluation reports will be available to the public under forthcoming Freedom of Information legislation. This legislation (due June 1994) will require Public Release Summary documents detailing the technical summaries of evaluation reports to be made available to the public. In anticipation of this legislation, the National Registration Authority has already implemented a policy to make the summaries publicly available. The public's access will however, remain limited to the summary report.

3.2 CANADA

Background on re-registration programme

Canada has both a re-evaluation (re-registration) and a renewal process for pesticides. Renewal, which occurs every five years (the length of all product registrations), is in effect a housekeeping exercise to update current registrations, but involves no data review. Re-evaluation involves an extensive updating and review of the database. Canada has been re-evaluating pesticides since the late 1960s. The programme was broadened and formalised in 1986 with development of an agenda for systematic re-evaluation of all registered chemicals following a priority ranking scheme. Every active ingredient was characterized and ranked for re-evaluation based on extent of use, age and completeness of supporting data, identified health concerns, and known or suspected environmental contamination. Under this ranking scheme, 469 registered active ingredients, involving 6095 products, have been prioritized for re-evaluation. Currently, 25 active ingredients are undergoing re-evaluation, a process that takes a minimum of 10 to 15 years to complete. Pesticides may also be identified for a special review or re-evaluation as a result of new information or evidence showing adverse effects, action taken or proposed in another country, or new information received through the Canadian Environmental Protection Act process.

Data review staff and process

Approximately 75 people in four departments are directly involved in evaluating registration data and preparing written reviews. The departments are Agriculture and Agri-

food Canada, Health Canada, Environment Canada, and Natural Resources Canada. While the majority of the staff are involved in new pesticide registrations, some 15 staff members will be involved in re-registration evaluations during fiscal year 1994: 7 for health reviews, 7 for environment reviews, 1 for forestry efficacy reviews. (Overall, there are 14 staff members involved in environmental/ecotoxicology data reviews, 33 in health reviews, and 28 in use/efficacy reviews.) There is no distinction between evaluators and re-evaluators, and data reviews for new registrations and re-registrations are done in the same way.

In Canada, pesticide registration is a consultative process. The Pesticides Directorate of Agriculture and Agri-food Canada is responsible for co-ordinating the data review. Once registration or re-registration submissions are received, the Directorate distributes the data for review by other federal departments as follows:

- Health Canada evaluates data on toxicology, residues, and occupational health and safety; advises Agriculture and Agri-food Canada on occupational safety and cautionary labelling statements; and sets maximum residue limits. These data evaluations are done by one group, the Foods Directorate, of Health Canada.

- Environment Canada evaluates fate and ecotoxicology data and provides advice on persistence, bioaccumulation, and impact on wildlife. One evaluation officer reviews the entire environmental package. Each re-evaluation focuses on one active ingredient. Evaluators do not specialize with respect to type of pesticide (e.g. herbicide), nor are they organized into groups that way.

- Natural Resources Canada and Fisheries and Oceans Canada provide information and advice on request to Environment Canada on specific issues associated with the impact on forest ecosystems and inland and estuarine fishery habitats, respectively. Natural Resources Canada also evaluates efficacy and benefits of forestry use pesticides.

- Various departments within Agriculture and Agri-food Canada review information on benefits, efficacy, and product chemistry and are responsible for the content of the registered label. Evaluation officers specialize in product types (vertebrate control, wood preservatives etc.) and are divided into four groups: Insecticides & Vertebrate Control; Fungicide, Fumigant & Biologicals; Herbicides & Plant Growth Regulators; and Antimicrobials.

  Evaluators in the four core departments (health, environment, agriculture, and natural resources) work independently in conducting their data reviews. In Health, the entire toxicology package is reviewed in one Division, usually by one toxicologist, although a team approach has been used on an emergency basis and will be examined further. Reviewers are encouraged to consult with fellow evaluation officers and make use of experts in the Department. Meetings with managers, senior staff and appropriate experts are held as necessary to finalize reports. In Environment, the entire data package is reviewed by one evaluator who is similarly encouraged to consult with fellow evaluators and experts within the Department. Meetings to discuss environment reviews occur after a draft report has been prepared. These peer reviews include other evaluators, all supervisors and experts within the Department, where appropriate. In Agriculture, evaluators work independently, though they consult colleagues in Research and Policy. Meetings are *ad hoc*; the responsible evaluation officer and appropriate experts are involved.

Each of these departments reviews the data in the context of the proposed use pattern, label directions and precautions. The departments then provide their advice/comments to the Plant Industry Directorate. At this stage, there is frequently extensive discussion and consultation between advisors, the applicant and occasionally invited experts. There is no formal process for determining which studies are most important; this is managed on a case-by-case basis. The results of data reviews in different scientific disciplines are integrated in Discussion or Decision Documents. Agriculture and Agri-food Canada is the lead agency and makes the final decision based on risk/benefit analysis.

Staff training is carried out differently in the four core departments. Agriculture has a strong, systematic training programme for new staff at all levels of the operation, with introductory lectures/presentations and apprenticeship to experienced staff members. Agriculture also provides continued training through seminars etc. and encourages attendance at scientific conferences. Health has no formal programme for new staff but provides training and apprenticeship on an *ad hoc* basis as necessary. Continued training is provided as budget and opportunities permit. In Environment, new staff receive on-the-job training from senior evaluation officers. New staff are also encouraged to consult with their colleagues, and all staff are encouraged to attend seminars and scientific conferences when funds are available. In Natural Resources, training is provided on the job. The multi-disciplinary review process results in new staff working with experienced staff in co-ordinating reviews.

Quality control

1. Consistency of reviews

Health does not use specific triggers or hazard levels to ensure consistency of data reviews, but rather uses line management (review of review documents by colleagues and senior staff). By contrast, staff of Environment, in reviewing data, consult with an internal document that lists different criteria to define levels of persistence, toxicity, volatility, leaching etc., to ensure consistency in the interpretation of data endpoints. Review of data on environmental chemistry is carried out with reference to the Canadian Guidelines for Determining Environmental Chemistry and Fate of Pesticides: these guidelines outline data requirements, suggest methods for generating and reporting the data, and describe how to predict exposure. Canadian environmental toxicology guidelines (documents outlining specific data requirements and suggesting methods for generating and reporting data) are in preparation and in the meantime other guidelines, e.g. those of U.S. EPA, OECD and Germany are consulted. Environment Canada staff, particularly new staff, also consult the U.S. EPA's Standard Evaluation procedures; these are a set of guidance documents which explain the procedures used to evaluate pesticide data, identify ways to treat scientific issues and provide interpretive policy guidance.

Canada has no external peer review process for its evaluations of health and environmental hazard, but it does have several internal review processes:

- For human health and safety reviews: All parts of the health assessment of pesticides, whether dealing with toxicology, dietary exposure, or occupational or bystander exposure, rely upon reviews that have been peer-reviewed by colleagues and supervisors. The peer review process is submission dependent, that is, the greater the concern for toxicity, the more extensive the peer review. All submission

evaluation reports are peer reviewed by at least one level of management. Where particular issues of concern are identified, they may be peer reviewed by experts in those areas and the final report would indicate the consensus of the panel of reviewers.

- For environmental chemistry and fate and environmental toxicology reviews: Peer reviews are held for each submission. Peer reviews include immediate supervisors (one level of management), other evaluators and, when appropriate, other scientific experts from within Environment Canada. No outside experts are involved.

- In Natural Resources Canada, evaluations are managed on a team review basis. The Team will include expertise in efficacy, value, environmental toxicology and fate. Individual reviews will be co-ordinated and then brought together for joint discussion and review.

- Based on the input from the other departments and its own analysis of benefits and efficacy, Agriculture develops regulatory proposals which are peer reviewed, considered by management, reviewed by the registrant, and subject to public consultation.

2. Data quality

It is not a legal requirement that studies submitted to support a pesticide registration follow national or international test guidelines, but this is strongly recommended and is true for the great majority of submissions received. Studies not following such guidelines are reviewed to determine whether the protocols used are scientifically supportable and a summary of that determination is included in submission data reviews. Recent reviews indicate whether studies follow specific test guidelines. This may not have been done consistently in the past; however, a description of methodology would generally be provided.

Health requires in principle that studies be done in compliance with GLP and that study submitters indicate whether each individual study was done according to GLP. This requirement is most strictly applied for animal toxicology studies. Studies not done according to GLP -- i.e. mostly older studies -- are treated with care and may only be used as supporting data. Evaluation reports always identify those studies that did not comply with GLP.

Environment does not require but encourages that studies be done according to GLP. Study submitters are not required to indicate whether each study was done by GLP, and data reviews do not specifically indicate this. However, the reviews will indicate if studies are rejected and the basis for that rejection. Non-GLP studies are accepted if scientifically sound.

Agriculture accepts non-GLP studies provided they are statistically valid; data reviews do not state GLP compliance but do provide the reason if certain studies are rejected.

Natural Resources does not require GLP for efficacy studies, but it is expected that studies will meet or exceed GLP standards.

Health Canada works co-operatively with the U.S. in conducting a laboratory monitoring programme to ensure GLP compliance (Canada notes that its own contribution is

minor). Environment and Agriculture do not monitor GLP. Significant fines and penalties are proposed in new legislation expected to go forward to government in 1994.

3. Data used/reviewed

Re-registration data reviews are comprehensive, including all data required for registrations. They also consider information from researchers within government agencies and academia, e.g. monitoring studies. Data in all test areas are evaluated simultaneously by the three core departments. Within test areas, data are also reviewed simultaneously (rather than in order of receipt) or will be in future.

Health and Environment Canada both use detailed data reports as a basis for their reviews; in addition, both routinely require raw data, e.g. Health requires individual animal data for all parameters assessed. Environment Canada also reviews papers published in scientific peer-reviewed journals. Health is exploring the use of certified summaries in conjunction with individual animal data. Agriculture Canada relies on summaries of individual studies, but also reviews detailed data reports and even raw data if questions arise. Natural Resources does not request raw data.

Health Canada re-examines old studies. Environment reviews but does not re-examine them if they were previously reviewed by the department; Environment would use conclusions from previous reviews towards the overall assessment. Agriculture does not re-examine old studies but considers the results of previous reviews. Natural Resources may re-review data if the assigned staff are not familiar with the older data.

4. Study documentation

All studies relating to human health and safety are logged into a computerized tracking system. Evaluation reports would also identify the studies. The tracking system does not indicate whether or not a study served as the basis for a regulatory decision; rather, individual reviewers are responsible for documenting which studies have been reviewed in their evaluation reports. For environmental data, study references are currently included in evaluation reports, but are not formally logged into a computerized tracking system. Agriculture also has no formal system, but reviewers are responsible for tracking which studies have been evaluated within the department.

Availability of reports

The public does not presently have access to Canada's full reviews; however, summaries are made available (through decision/discussion documents). Data protection and public access are being discussed and may be revised under proposed new legislation. Other governments have recently been given access to full reviews under the OECD pilot project, with registrant permission.

3.3 DENMARK

Background on re-registration programme

Denmark's re-registration programme applies to both old and new pesticides. In 1987 Denmark established a 5-year re-registration programme for all pesticides registered before the Act on Chemical Substances and Products came into force in 1980. Pesticides designated for re-registration were grouped according to their most common use (e.g. herbicides in grain). The groups were prioritized according to extent of use and the amount of active ingredient sold and, to a certain extent, chemical similarity (e.g. phenoxy acids).

Since 1988 all registrations for new active substances have been granted for a period of 8 years or less, with re-registration subsequently required. Toxic and very toxic products (as defined in Directive 78/631/EEC) must be re-registered after 4 years. The date for re-registration is stated in the registration document.

Re-registration data reviews are done the same way as new registration data reviews. Data requirements for re-registration are set out in the Statutory Order on Pesticides of 10 December 1987.

Data review staff and process

In Denmark the pesticide registration authority is the Danish Environmental Protection Agency. As the re-registration programme runs for 5 years from 1988 to 1992, a number of staff members are employed for this specific task for a limited period. Five staff members are directly involved in evaluating pesticide re-registration data and preparing written reviews. In addition, some evaluations are done by external consultants. The re-registration staff are different from staff involved in evaluation of data for new pesticide registrations.

Re-registration data review staff work independently in two groups: two persons review all toxicology data and three review all ecotoxicology data including physical chemistry. The two teams hold meetings on an *ad hoc* basis. General meetings for all re-registration data review staff are held once a month.

To help assure consistency and quality of reviews, Denmark provides new staff with general introductory training and has them work closely with experienced staff. Denmark has no specific continuing training programme, but relevant courses may be granted by request.

Quality control

1. Consistency of reviews

Before 26 July 1993 Denmark used established guidelines that set hazard triggers for toxicological effects and some ecotoxicological effects (e.g. leaching and persistence). With the implementation of Directive 91/414/EEC for plant protection products, however, evaluations will be done according to a risk assessment. In the transitional period, i.e. as long as the active substances are not on Annex I to Directive 91/414/EEC, a guidance document

will be written with some triggers for ecotoxicology and a risk evaluation for toxicology. The new guidance will also be used for the substances under re-registration for which a decision has not been made before 26 July 1993.

Denmark does not have a formal peer review system. However, all reports made by external consultants are checked by the review staff in the office. Reports judged unacceptable are required to be redone. If there are special problems with the substance, external experts (from other ministries, universities, etc.) are asked for their opinion.

2. Data quality

Denmark has previously required only toxicology studies to be done in compliance with GLP; however, from 26 July 1993, under the EEC Directive 91/414, GLP will be required for most studies done to support the registration of plant protection products. Denmark requires study submitters to indicate whether each individual study was done according to GLP, and Denmark's reviews indicate whether or not the studies complied with GLP. Studies not done according to GLP are evaluated on a case-by-case basis.

Denmark's National Agency of Industry and Trade is responsible for GLP inspection of Danish laboratories; laboratories in other countries are not inspected by Danish authorities and their credibility is not verified. Denmark may impose fines or other penalties for falsifying data on a general basis under the Act on Criminal Code.

Denmark requires studies to follow international guidelines, preferably those of OECD or EEC, but other guidelines (e.g. U.S. EPA) are sometimes accepted as well. Studies which do not follow international test guidelines are evaluated critically and included in the review report, with an indication as to whether the study is acceptable or not. The data review also indicates which guideline the study followed.

3. Data used/reviewed

When a substance is evaluated, all studies will normally be reviewed. In certain instances, however, if there are many studies covering one topic, e.g. residue studies or gene mutation studies, only some of these studies will be evaluated in depth and referred to in the review report. Efficacy is considered as well as hazard and risk. Data in all test areas are reviewed simultaneously. Old studies are re-examined only if they are referred to in the re-registration application and if they are not replaced by new studies.

Denmark does not rely on data summaries but reviews the original reports of the studies. On rare occasions, raw data such as slides or lab books are requested.

4. Study documentation

The system for documenting all studies evaluated consists of the reference list for each active ingredient. Denmark does not have a computerized tracking system.

Availability of reports

Data review reports are not normally provided to the public, but they can be sent to other ministries. Summaries and evaluations of the studies are given in the registration decision which is sent to the applicant, and this decision can also be sent to the public or other interested parties on request.

3.4 FINLAND

Background on re-registration programme

In Finland, the re-registration of pesticides is a housekeeping exercise to update registrations, since pesticide products are registered for a maximum of 8 years. Depending on the toxicological and ecotoxicological nature of the active ingredient and the status of the submitted documents, the re-evaluations can be comprehensive, including all data, or they can be short, including only new data and serving to update the existing review. If a Finnish evaluation of the active ingredient already exists and is considered to be relevant, the whole package of documentation is generally not re-reviewed due to scarce resources. Finland also co-operates closely with the other Nordic countries in the form of joint toxicological and ecotoxicological evaluations, for both registration and re-registration of pesticides.

Registration and re-registration decisions are made by the Pesticide Commission which is composed of representatives from the Ministry of Agriculture and Forestry, the Plant Production Inspection Centre, the Ministry of Social Affairs and Health, the National Board of Waters and the Environment, the Ministry of Labour, and the National Food Administration. The Plant Production Inspection Centre, which acts as secretariat for the Pesticide Commission, co-ordinates the process. Health and environmental data are evaluated by the authority with the appropriate expertise, i.e. the Ministry of Social Affairs and Health evaluates data on toxicology, residues, and exposure; the Ministry of Labour examines labour protection; the National Board of Waters and the Environment evaluates ecotoxicology and environmental fate; and the Agricultural Research Centre evaluates efficacy for first-time registrations and, in special cases, for re-registrations. These authorities make their evaluations independently and give their opinions on the acceptability of the pesticide to the Pesticide Commission, which makes the final decision after considering all relevant information, i.e. hazard, exposure, efficacy, and need/benefit.

The Pesticide Commission produces annually a programme with prioritization of old pesticides to be evaluated during that year. Priorities are based on properties of the pesticide (adverse effects), international actions, the availability of new studies to support the registration, and attempts to reduce the use and/or use rates of certain groups of pesticides (for example, in 1994 Finland is re-evaluating all herbicides for potato and all growth regulators for cereal). In addition to this prioritization, a number of pesticides must be re-evaluated and re-registered each year due to expiration of their registration.

Data review staff and process

Eight staff members are directly involved in evaluating pesticide re-registration data and preparing written reviews: four staff members in the Ministry of Social Affairs and Health review toxicology data; four staff members in the National Board of Waters and Environment review ecotoxicology. In addition, three staff members in the Agricultural Research Centre review efficacy (if needed) and one staff member in the Ministry of Labour reviews labour protection. These authorities, however, do not produce separate evaluations but merely a statement (2-4 pages). Efficacy is normally evaluated only for first-time registrations except in special cases, e.g. a proposed reduction in use rates. Physical-chemical data are not in general evaluated separately. Occupational exposure studies, if submitted, are usually evaluated in the toxicological review by the Ministry of Social Affairs and Health.

These twelve principal data reviewers are the same people who conduct data reviews for new pesticide registrations. In general, one person in each unit carries out the whole evaluation for that field. Only in the Plant Production Inspection Centre and the Agricultural Research Centre are staff organized according to the type of pesticide (insecticide, fungicide, herbicide, and growth regulator). Consultants may also be involved or outside experts consulted.

The staff members work quite independently when evaluating the data and preparing draft reviews, but meetings are also organised on an *ad hoc* basis. Ecotoxicology evaluations are always reviewed internally by the National Board of Waters and the Environment, before an official statement is given. The toxicology evaluations are reviewed internally or, in most cases, in a peer review process. The peer review involves an Expert Group of Toxicology that is composed of seven academics representing different fields of toxicology. This group is actually involved both during and after the data review: it gives advice in conducting the evaluation, reviews evaluation documents written by government staff or consultants, and provides a written summary of the adverse effects and a conclusion to the Ministry of Social Affairs and Health. A second expert group, the Council for the Evaluation of Health Hazards of Chemicals, may also become involved in cases where a conflict is anticipated between the Pesticide Commission and the registrant over a registration or re-registration decision. This council reviews the relevant original studies independently, and provides a statement of its conclusions to the Ministry of Social Affairs and Health. As with the Expert Group of Toxicology, the Council for the Evaluation of Health Hazards is composed of toxicologists representing different areas of expertise; both groups works under the Ministry of Social Affairs and Health.

Finland does not have systematic training for staff who evaluate pesticide data, although new staff receive an introduction to the programme on an individual basis. Finland does not have a formal apprenticeship system for new staff, but in practice, experienced staff members help beginners. Staff are encouraged to discuss problems and consult different academic and research institutions. The staff also have the possibility to attend international scientific congresses for educational purposes. Expert lecturers are invited and courses arranged within the ministries for continuing education and training of all staff.

In general, re-registration data reviews are done in the same way as new registration reviews. Data in all test areas are in principle reviewed simultaneously by different authorities to gain the registration/re-registration as soon as possible. If necessary, the results of the evaluations in different test areas are integrated by the Pesticide Commission, which also decides on approval or non-approval of the pesticide.

Quality control

1. Consistency of reviews

Finland's data reviews follow the Nordic format (designating the structure of the reports) agreed with Sweden, Norway and Denmark. Finland has not yet established specific triggers for risk concerns and thus uses a more flexible, case-by-case approach. Finland notes that OECD test guidelines provide some guidance for interpreting results, although to a limited degree. Finland also note that the interpretation of results is in practice rather constant. The reviews are aimed to identify the hazard and the possible risk; there is no attempt to quantify risk. The quality and consistency of Finland's ecotoxicology reviews are assured through the internal review process, and of the toxicological reviews, through internal or (in most cases) a peer review process.

2. Data quality

Finland's pesticide act does not explicitly require compliance with GLP; however, a general GLP requirement is mentioned in the application form. Finland notes that in the case of environmental fate, there are usually no GLP studies available. Study submitters are required to indicate whether each individual study was done according to GLP, and Finland's toxicological data reviews in general indicate compliance or non-compliance with GLP in the beginning of the review. Studies not done according to GLP are evaluated on a case-by-case basis. Greater significance is given to studies in the same test area which have been done according to GLP; however, Finland notes that it is better to have non GLP-studies than no studies at all.

Finland also considers whether studies have been done according to accepted test guidelines. Finland favours the OECD guidelines, but also accepts studies conducted according to US-EPA and European Commission guidelines. (In the management of chemicals in general, the EC legislation is already implemented in Finland.) Since there is an increasing need for ecotoxicological studies, for which OECD guidelines have not yet been developed, studies conducted according to German BBA are also accepted. Studies that do not follow requested guidelines are usually included in the review, if no other study done according to a generally accepted guideline is available. Data reviews should (but do not always) mention whether studies were used to support the registration.

If all studies are done according to OECD test guidelines, this is mentioned as a general statement in the beginning of toxicological reviews (this is mostly the case with new substances, however). Ecotoxicological evaluations indicate whether or not individual studies follow OECD or other known test guidelines. Finland notes its interest in improving its way of indicating whether or not studies follow specific test guidelines.

In the area of toxicology, Finland has had programmes since 1990 for inspecting and auditing laboratories to ensure that their studies are conducted in accordance with GLP. The Ministry of Social Affairs and Health is the monitoring authority; the National Agency for Drugs is the institution that carries out GLP inspection in Finnish laboratories. Laboratories in other countries are not inspected, but information about the inspections in other countries are received through OECD. Finland notes that there are currently no official GLP laboratories

in environmental studies. Under general criminal legislation, Finland can issue fines or other penalties for falsifying data.

3. Data used/reviewed

Data requirements for re-registration depend on the pesticide in question and its properties, use, residues, toxicological and ecotoxicological profiles etc. Thus the requirements are more or less on a case-by-case basis. If there are no new data available, and old documentation previously evaluated is considered adequate, the review can be short or may not be needed at all. In principle, all available data are used in the review process; old studies are not rejected just because they are old. Finland does not rely on data summaries but always asks for the original study reports.

In considering pesticides for re-registration, Finland considers efficacy, available alternatives and application, in addition to hazard and risk. According to Finland's pesticides act, a product must in principle be approved if there are no adverse effects on health and/or the environment.

4. Study documentation

Finland currently has no register of the studies evaluated and accepted. To find out what studies were used in the evaluation, one must go back to the reference list of the review in question. If the study was rejected, this should be (but is not always) mentioned in the review.

Availability of reports

Finland's data review reports are available to the other Nordic countries and, on request, can be translated if they are available in Finnish only. So-called Nordic evaluations are written in English or Swedish. The evaluation reports are not released to the public, but the statements are public.

3.5 GERMANY

Background on re-registration programme

Germany does not have a re-registration programme in the sense in which this is generally understood. Rather, Germany has a system that requires all pesticide authorizations to be periodically renewed. Under Germany's Plant Protection Act, pesticide authorizations are granted for a maximum of 10 years. When an authorization expires the registrant must re-apply, submitting all data required for authorization at that time. Germany is continually updating its pesticide data requirements; thus the data files on existing compounds grow with every application for renewal.

The schedule for renewing pesticides is based primarily on the date of the original authorization, but also takes into consideration health and environmental concerns. Germany also has the authority to withdraw authorizations or to require additional data during the authorization period, and to grant authorizations for a limited period -- while awaiting results from long-term studies or international re-evaluations, for example. Authorization decisions consider not only risk but also uses and efficacy.

The authority responsible for authorizing plant protection products in Germany is the Federal Biological Research Centre for Agriculture and Forestry (BBA). The authorization process within the BBA is run by the Department for Plant Protection Products and Application Techniques. The BBA must act in agreement with the Federal Health Office (BGA) where health is concerned (e.g. BGA sets maximum residue limits) and the Federal Environmental Office (UBA) with regard to the prevention of damage resulting from water and air pollution or waste disposal. BBA thus co-ordinates the review and approval process, with participation of BGA and UBA in certain test areas.

Data review staff and process

The overall number of scientists directly involved in evaluating pesticide data and preparing written reviews is about 44-50, not counting technical assistance (roughly the same number again). This staff is organised as follows:

BBA: Within the Department for Plant Protection Products and Application Techniques, the two divisions which are involved in data evaluation, the Biology Division and the Chemistry Division, each employ 14-16 scientists and supporting technical staff. The department management also has 6 scientists, along with 2 lawyers, 10 computer staff, 9 administrative staff and secretarial/technical support. Scientific staff involved in reviewing pesticide data include the following:

efficacy:	6
(responsibilities distributed by crop and type of compound)	
physical-chemical properties:	2
analytical methods:	2
residues:	4
environmental fate:	3
honey bees and beneficial arthropods:	1
earthworms:	2
terrestrial vertebrates:	1
aquatic organisms:	2
soil microflora:	1

Apart from efficacy, the responsibilities are split by the type of compound (insecticide, herbicide etc). These scientists work on all applications, whether for a new product, renewal of an existing authorization, or new uses of an old product. The scientists also write review reports, issue requirements, and discuss matters with the registrants/manufacturers. They are supported in their work by scientists of the specific research institutes of the BBA dealing with questions of plant protection, harmful organisms, and alternative products.

BGA: In the BGA, 11 staff members, all scientists, are directly involved in evaluating pesticide authorization data and preparing written reviews. They are organized in four groups dealing with:

toxicology/metabolism
operator exposure
ecotoxicology (fish)
residues in foodstuffs and MRL recommendations.

UBA: Thirteen staff members including 5 scientists are directly involved in pesticide data reviews. They are organized in four groups as follows:

exposure analysis (environmental fate, physical-chemical properties, metabolism):	3
effects analysis (ecotoxicology):	4
risk assessment:	3
administrative work:	4

Scientists in each of these groups review the data that correspond to their area of expertise. The scientists also hold discussions with applicants as necessary, regarding the validity of studies or the need to submit additional data. Although it is not required, scientists in BBA and BGA may draft notes or summary reviews of the data (a "raw" data review). UBA does not contribute written notes apart from informing BBA of their decision regarding labelling; however, data reviewed by UBA are also reviewed by BBA. Scientists also write a recommendation regarding approval/non-approval of the registration. The reviews and recommendations are collected in a pesticide dossier which is organised by BBA. After the evaluation in each area is complete and before a final decision can be made, the dossier containing the raw data reviews, results and proposals for decision is presented to an advisory group of 25 external experts (Committee of Experts, SVA). These experts come from the extension services of the federal states (Länder), other Länder or federal authorities, universities, or other research institutions (with numbers from each group in that order).

Within BBA and UBA, each study is reviewed by one scientist; in BGA, studies are reviewed by two scientists. The members of the toxicology/metabolism group of the BGA meet once a week to discuss their conclusions about the data. In all other groups in BGA, UBA and BBA, meetings are held on an ad-hoc basis.

Germany provides a general introductory training for new staff in each agency, emphasizing overall goals of authorization and re-registration and providing information on the relevant laws, administrative procedures etc. New staff members are assigned to an experienced staff member for systematic training in how to evaluate pesticide data and prepare written reviews, based on Germany's criteria and procedures. This is done as an apprenticeship, lasting several months.

Continuing training in toxicology, pathology and metabolism is provided for scientists in BGA; the other agencies are not able to provide such training due to lack of funds.

Quality control

1. Consistency of reviews

Germany's data reviews are done in accordance with criteria set out in the "yellow booklet," the Criteria for Assessment of Plant Protection Products in the Registration Procedure. These criteria are based on specific hazard levels indicating risk concerns for different endpoints. Hazard levels can be either absolute values (mostly environmental fate, i.e. certain degradation times or concentration in ground water) or a toxicity/exposure ratio (ecotoxicology). The criteria include the uniform principles for toxicological assessment written by BGA, and principles for assessments in all other test areas written by BBA.

There is some flexibility in applying established hazard levels; a pesticide will not automatically be rejected if a level is exceeded. This flexibility is established by both the Plant Protection Act and the final "Paraquat" judgement of the Federal Administrative Court (the highest legal decision for such matters), which state that regulatory decisions on pesticides must be based on a risk/benefit analysis in all cases except those involving human and livestock health and ground water. Thus, the hazard levels for carcinogenicity, genotoxicity, teratogenicity and reproductive toxicity are applied more strictly than in other test areas.

2. Data quality

Germany requires all studies in all test disciplines started after 1/4/90 to be done in compliance with international GLP principles. Studies started after this date that do not follow GLP principles must be rejected. Older studies, i.e. those started before 1/4/90, that were not done according to GLP must be accepted under certain conditions, e.g. if they were completed by specified dates or if the competent authority judges them to be acceptable with regard to GLP principles. Studies which were not done according to GLP are given less importance in regulatory decision making.

Germany's internal "raw" data reviews indicate whether or not the studies complied with GLP. However, this information is currently not included in the summary reviews (dossiers) which are submitted to the Committee of Experts.

Guidelines for each test are recommended or prescribed by BBA (in BBA Guideline Part I, 1-2: Application for registration and re-registration of a plant protection product -- directions for completion). Depending on availability, these are either OECD, CIPAC, IPBC, BBA or other guidelines (e.g. EPPO, ISO). The BBA Guideline also states that other guidelines than those recommended might be used but will be evaluated carefully (these could include for example EPA guidelines). Acceptance depends on similarity of study design, importance of this particular endpoint for the risk characterisation etc. Acceptance is case by case, but the rate of acceptance is high. The BBA Guidelines has been periodically updated but in future will be replaced with a guidance adapted to the EC registration system.

The pesticide dossier does not usually state what test guidelines were used, as the dossier is prepared for internal use by staff who would know the appropriate guideline. Dossiers would only note instances in which a guideline allows for different designs, e.g. aquatic testing: semistatic vs. flow-through. In addition, some reviewers keep notes of such information for their own use.

Germany has a monitoring programme for inspecting and auditing laboratories to ensure that their studies are conducted in accordance with GLP. The federal states (Länder) are responsible for inspecting laboratories and issuing GLP certificates. These certificates list the studies which a lab can perform according to GLP principles. If the lab wants to perform other tests a new inspection is required. Länder authorities generally do laboratory inspections on a routine basis (e.g. every 2-3 years), although they can also do unscheduled inspections and can inspect a lab if requested by BGA, UBA or BBA.

Germany can impose fines or other penalties (sentence up to five years) for falsifying data, under the Criminal Code.

3. Data used/reviewed

In the renewal (re-registration) process the detailed data reports as well as the data summaries are reviewed. In case of difficulties in interpreting the results of a study, raw data, such as historical control data, and additional evaluations by independent experts are requested. Lab books are sometimes required if there are doubts about the reliability or validity of a study. Samples are regularly requested for the evaluation of physical-chemical properties. All old studies are re-examined, including those studies that were previously reviewed for registration. In principle, the data review is done in all areas simultaneously and in order of receipt; however, reviews in some areas must await the outcome of information or results from others.

4. Study documentation

Germany documents both the studies that have been reviewed (this is done by the individual reviewers in their reports to the pesticide dossier) and the studies which served as the basis for a regulatory decision.

Availability of reports

Under the current system, the German dossier is not available to the public. The Plant Protection Act does not provide for release of this information: the data are considered confidential property of the company, and the dossier was never meant to be used outside the regulatory authorities and committee of experts. Only the decision with all the labelling and use restrictions is published (in the Federal Gazette). For the purposes of the OECD Pilot Project to Compare Pesticide Data Reviews, permission from the companies concerned was necessary. Also, most data concerning individual products (efficacy, labellings, residues etc) were deleted from the dossiers.

With the implementation of EC Directive 91/414/EEC, which provides for the release of evaluated data concerning health and environmental effects, Germany will adopt a different approach.

3.6 THE NETHERLANDS

Background on re-registration programme

Re-registration of pesticides in the Netherlands began in 1988, when the Advisory Centre for Toxicology at the National Institute for Public Health and Environmental Protection (RIVM/ACT) started the project Catch-up Operation on Old Pesticides. The project aimed only at the evaluation of environmental aspects of already registered pesticides. The catch-up of toxicological aspects of old pesticides was performed in a separate project that started three years later and that lasted for two years (the main purpose of this project was to catch up with the first in having available an up-to-date summary and evaluation). During these years, only a limited number of substances could be evaluated. The project to evaluate environmental aspects is scheduled to be completed by mid-1994. The re-registration projects have included approximately 200 agricultural and 100 non-agricultural pesticides.

For each substance in the re-registration projects, a summary of available data on toxicology and ecotoxicology and an evaluation of these data were prepared and reported in separate reports (these reports are available on request to governmental organisations and international non-profit institutions). Pesticides meeting at least one of the following criteria were required to undergo re-registration:

- already on the Dutch market before 1975,
- proven problem substance because of environmental properties,
- registration expiration in 1987-89,
- substantial production or market volume in The Netherlands,
- environmental summary absent or incomplete.

Data review staff and process

Because of the short-term nature of the Netherlands' re-registration programme, different staff have been used to conduct re-registration data reviews vs. new registration reviews. For the re-registration programme, a number of staff were hired for a period of three years or less to work under the guidance of the permanent staff of the Advisory Centre for Toxicology. The table below shows the number of people involved in re-registration and registration of pesticides. The numbers in brackets reflect the reduction in re-registration staff for ecotoxicology after the first three years of the project (e.g. total ecotoxicology staff for re-registration were reduced from 14 to 4). The toxicology part of the re-registration project was stopped after two years.

	ecotoxicology	toxicology
Re-registration	14(4)	7
- academic	12(3)	6
- administrative	2(1)	1
Regular	6	6
- academic	2	2
- non-academic	3	3
- administrative	1	1

Although the re-registration and registration staff are different, the data reviews themselves have been done in the same way. Data review staff work independently in reviewing data on a substance, but the staff also function as a team, and their work receives several rounds of review. Staff are divided into teams -- toxicology and ecotoxicology -- each headed by a scientific project leader. Teams meet once a week to discuss data review summaries and once to discuss scientific and managerial aspects of the work. Additional ad hoc meetings are also arranged if necessary. Problems and issues are discussed by the team to help ensure consistency in how different team members approach similar situations. Meetings are recorded for future use by other workers. Data review staff can also discuss the information individually with the scientific project leader and with experts in the field.

RIVM's standard education procedure for new staff includes a general introduction to the registration and re-registration programme, assignment (apprenticeship) to an experienced staff member, and training in specific fields of interest by in-house experts. All staff have the opportunity for continuing education outside the department.

The data review documents, called concept reviews, provide risk indications (public health, occupational, and environmental) and consider efficacy, but they do not make recommendations regarding registration. These recommendations are made by an Advisory Board made up of RIVM staff and experts from other Dutch institutions representing the disciplines of organic chemistry, environmental chemistry, soil chemistry, aquatic ecotoxicology and terrestrial ecotoxicology. The Advisory Board discusses the concept reviews thoroughly and makes a recommendation regarding registration. The advice of the Advisory Board serves as the basis for preparation of final documents which are considered first by a separate board of independent, non-government scientists, and finally by the government Pesticide Registration Board, which makes the registration decision.

Quality control

1. Consistency of reviews

To ensure that different reviewers use a common approach in reviewing data and evaluating pesticides, all new workers receive detailed instruction on RIVM's rules and

guidelines, including hazard levels or triggers. Quality and consistency are also insured by the involvement of the scientific project leaders, who are co-authors of every data review.

RIVM has established triggers or hazard levels and applies them very strictly: these levels are cited in reports (e.g. RIVM report no 678801002, Canton et al., 1991) and are freely available. Substances which hit the hazard levels are placed on so-called sanitation lists and will be the subject of a banning procedure. (The banning procedure allows the company to deliver additional data, negotiate with the evaluating authorities, propose additional research, or initiate a court procedure to attempt to reverse the ban.) Areas where triggers are most strictly applied are degradation time (DT_{50} < 180 days), leaching to ground water (C_{leach} < 0.1 μg/l), and toxicity to water organisms (PEC/NEC < 1). Criteria for other endpoints are currently under development.

RIVM has developed draft guidance for reviewing pesticide data, to assist reviewers in judging whether studies have been done well, have met key criteria (e.g. proper soil temperature), and whether results are reliable. Studies which do not meet the important criteria are not necessarily rejected but are given less weight in the hazard assessment.

2. Data quality

RIVM has in principle required compliance with GLP principles for studies in all test disciplines since July 1991. This requirement is not yet strictly applied, however. Studies not performed according to GLP may be included in data reviews, and given as much weight as GLP-compliant studies, if they meet all relevant criteria for the specific details of the study. Data reviewers judge the quality of each study and record their judgement in the data review summary, where studies are categorized in the bibliography: "1" for a well performed study meeting all criteria; "2" for studies not meeting all criteria but that could be taken into account when category 1 data are missing; and "3" for summary reports and other information. The Netherlands does not require study submitters to indicate whether each individual study was done according to GLP; however, reviews indicate generally whether studies complied with GLP, and they note cases where the study submitter failed to indicate GLP compliance.

RIVM does not have a laboratory monitoring programme to ensure that studies are conducted in compliance with GLP. However, the Quality Assurance Unit of RIVM can be asked to audit labs claiming GLP compliance, with or without suspicion that GLP might not be strictly followed. RIVM cannot issue fines or other penalties for falsifying data; however, such data would be excluded from the review. RIVM does not require that studies be done according to national or international test guidelines; studies following RIVM's in-house guidelines are also accepted.

3. Data used/reviewed

Data reviews for re-registration are done the same way as reviews for new registrations. Old studies are generally included in the reviews, although they are scrutinized if there are doubts about validity. Reviews are never based on data summaries; complete reports are always required. If the reports raise questions, clarification is requested from the applicant. There is no specific order in which data are to be reviewed: the available data are gathered and the reviewer determines the order of review.

Decision making on a pesticide includes information on benefits, efficacy, and availability of alternative pesticides, as well as on public health, occupational and environmental risk. In addition, the Netherlands has recently adopted a policy requiring that availability of alternative methods for pest control be taken into account. Registration decisions are taken by the Pesticide Registration Board, which includes policy staff of the Ministries of Agriculture, Public Works and Environment, Health, and Social Affairs.

4. Study documentation

All reviews are stored in a computerized database called TOXBANK, where they are filed in a consistent format. Because the system is substance oriented, a bibliography of reviewed reports and review dates is included for every substance. In addition, it is possible to use the database to make cross references among substances and to compare data on specific properties. TOXBANK currently contains information on approximately 350 pesticides.

Availability of reports

Concept reviews, containing all information about the pesticide except composition of formulations, are available on request to governmental organisations and international non-profit institutions. RIVM notes that exchange of reviews among such organisations is frequent. In addition, reviews are sometimes shared with developing countries. By contrast, full review reports are not available to the public. For distribution to the public, RIVM publishes separately a paragraph containing all conclusions about the pesticide hazard, its possible risks, and classification of its inherent properties.

3.7 NEW ZEALAND

Background on re-registration programme

New Zealand does not have a formal re-registration programme, but reviews pesticides on an *ad hoc* basis, where concerns or actions by other countries are of relevance to the use of the pesticide in New Zealand, or where local information suggests there may be grounds for revoking registration. Any such review covers all aspects of health and environmental impacts of the pesticide, and includes consideration of less hazardous alternatives, options for risk/exposure reduction, and mechanisms for enforcement of decisions. Registration and re-registration decisions on pesticides are made by New Zealand's Pesticides Board, based on recommendations made by the data review staff of the Ministry of Agriculture and Fisheries. The Pesticides Board, established under the Pesticides Act 1979, consists of representatives from the major government departments, the pesticide industry, and various user groups. The Board normally accepts the recommendations made by the agriculture ministry, but it often asks searching questions and sometimes defers a registration until more information is available.

Data review staff and process

Five staff members of the agriculture ministry are involved in reviewing pesticide registration and re-registration data and preparing written reviews: two cover toxicology and environmental toxicology data, one covers residue data, and two cover information on efficacy. Consultants (e.g. staff from the Ministry of Health) may also be used when expertise in other areas is needed. The data review group function as a team, holding information meetings and discussions and preparing reports/recommendations for the Pesticides Board.

The data review begins with an initial review of data summaries in order to get an overall picture. Then, depending on what is found in the summaries, staff may check the original study reports to ensure that summaries are accurate. Hazard and risk make up the major part of the review/decision, but the registrant must also show that the pesticide is efficacious and he must propose a "prudent and safe" method of application. All data are reviewed simultaneously.

New Zealand has little staff turnover, so there is no formal training programme or apprenticeship system for new staff. Instead, new staff work under the direction of an experienced staff member for 2-3 years. All staff attend conferences on pesticide issues as part of their job and continuing education. Advice from consultants is screened by government staff. In future, New Zealand intends to develop training programmes.

Quality control

1. Consistency of reviews

New Zealand has not established its own hazard levels or triggers, but applies the standards and criteria that have been set by other national or international bodies, including IPCS, WHO, OECD and U.S. EPA. New Zealand notes that they maintain close contact with U.S. EPA and others. Reviewers have flexibility in applying others' levels, however, adapting them to local needs and conditions. Consistency among reviews is achieved through use of an established data review system, including examination of the reviews by the Pesticides Board, and also by virtue of the fact that the staff is so small -- generally one person alone is reviewing data in a certain area.

2. Data quality

New Zealand requires toxicology studies to be done in compliance with GLP principles, and plans to extend this requirement to data on environmental impact and residues. Registrants are required to indicate GLP compliance (New Zealand notes that studies usually contain a certificate of GLP compliance). Non-GLP studies are assessed on a case-by-case basis; a study would generally not be accepted if it deviated too much from GLP and were key to the hazard assessment. New Zealand's reviews indicate whether studies complied with GLP, and whether international (or other) test guidelines were followed.

New Zealand's policy is that submitted studies must follow internationally agreed (i.e. OECD) test guidelines. **All** data submitted are included in reviews, but those that do not comply with the international guidelines are accorded less weight. New Zealand is reviewing

the format of its data review reports and now requires all reports to state whether OECD test guidelines were followed.

New Zealand does not have a laboratory monitoring programme because few data are produced in the country; systems are being developed, however, to test specific local species. To verify the credibility of GLP claims, New Zealand considers whether studies have been accepted by other national authorities that do have monitoring programmes. New Zealand has no specific legislation authorizing fines for falsifying data, but if such problems were discovered, registrations could be revoked or denied.

3. Data used/reviewed

Data reviews are done the same way as reviews for new registrations, but more emphasis is given to the issues that brought the pesticide into review, especially with regard to toxicity and efficacy. All available data are examined, including old studies, and new data may be requested from the registrant.

4. Study documentation

New Zealand has a computerized system for keeping track of studies that have been reviewed as well as the data reviews themselves. The system does indicate whether any particular study was the reason for refusal or restriction of the registration. The documentation system is currently being improved.

Availability of reports

New Zealand regards its data review reports as being subject to its Official Information Act 1982, and therefore available to the public on request. The reports are also freely available to other regulatory authorities. Any commercially sensitive information (such as formulation details) would be blacked out of a report before release.

3.8 NORWAY

Background on re-registration programme

Re-registration of pesticides (plant protection uses only) in Norway has been an ongoing programme since adoption of the Pesticides Act in 1963. This law stipulates that pesticide approvals will only be valid for 5 years unless otherwise decided at the time of approval. Products have therefore been required to undergo re-review and re-approval on a continuing basis.

Data review staff and process

Three staff members in the National Agricultural Inspection Service (NAIS) are directly involved in evaluating pesticide re-registration data and preparing written reviews: one reviews ecotoxicology data; the other two review toxicology and metabolism data. In addition, one or two staff members review use and efficacy, based mostly on data produced by the Norwegian Plant Protection Institute. The NAIS is an institution directed by the Ministry of Agriculture, dealing with approval and regulation of pesticides, fertilisers, feed, seed, plant health and so on. The NAIS is in charge of co-ordinating the process of re-registration of old pesticides and approval of new pesticides. Data review staff evaluate data both for re-registration and for new approvals. These staff work independently in conducting their reviews. Staff turnover is low; new staff members are trained through an apprenticeship system.

In decision-making on a pesticide, benefits to agriculture, availability of alternatives, and toxicological and ecotoxicological properties of alternatives are considered along with hazard and risk of the pesticide in question. Data in all test areas are reviewed simultaneously.

Quality control

1. Consistency of reviews

Norway is in the process of developing data review guidelines/procedures and expects to complete them by mid-1994. Currently, Norway does not have absolute criteria or cut-off values for the evaluation of pesticides, although fixed criteria are used for labelling purposes. Genotoxicity and carcinogenicity are evaluated most strictly.

Data review reports produced by Norway are reviewed, before they are made final, by an expert committee called the Pesticide Council which serves as an advisory board to the NAIS concerning pesticides. The Council is composed of scientists representing a range of disciplines (health, natural environment, genetics, agriculture, economics) and coming from other government ministries as well as non-governmental institutions. The Council may indicate, for example, that it is not satisfied with the information available on a pesticide and that more data must be submitted. The Council meets four times a year, reviewing approximately 5 pesticides at each meeting. Although its review is less formal than a peer review, the Ministry of Agriculture will not make a registration decision on a pesticide before the Council has considered and commented on the data review reports.

2. Data quality

Norway does not require studies to be undertaken in compliance with GLP principles, and study submitters are not required to indicate whether each individual study was done according to GLP. However, studies not in compliance with GLP are not considered as valuable as those which are. Non-GLP studies are evaluated on a case-by-case basis: if too far from GLP, they are given little significance in the data review. Norway's data reviews indicate whether or not studies complied with GLP.

Norway requires that studies submitted to support a pesticide registration follow accepted test guidelines: toxicology data are generally done according to OECD guidelines while ecotoxicology studies done according to German BBA, U.S. EPA and OECD guidelines have been accepted. Norway's data reviews indicate which guideline the studies followed. Old data are often included in reviews even if they do not follow test guidelines. In such cases this is noted in the report.

Norway does not currently have a laboratory monitoring programme, but is in the process of developing a quality standard including penalties for falsifying data.

3. Data used/reviewed

Re-registration reviews include a re-examination of all old studies, and writing of a new summary report of 10-15 pages. Data reviews are based on full study reports, not summaries.

4. Study documentation

Norway has an internal system for keeping track of studies that have been reviewed and for indicating whether or not a study served as the basis for a regulatory decision.

Availability of reports

Norway's data review reports are considered confidential because they contain information about formulation, synthesis and so on. The members of the Pesticide Council and the applicant are the only outside persons who have access to the reports.

3.9 SWEDEN

Background on re-registration programme

Re-registration is part of a general pesticide risk-reduction programme developed by Sweden's Chemicals Inspectorate (KemI), the government agency responsible for approving pesticides, together with the Environmental Protection Agency and the Board of Agriculture. Sweden's re-registration programme applies to all pesticides holding a registration older than 5 years. Products may only be approved for a 5-year period, after which a renewal of the registration is required. Products registered before 1986 are being re-registered for the first time during 1990-94. Priorities for re-registration are thus primarily chronological, but they can also be based on high use (e.g. herbicides) or suspected health or environmental concerns.

Data review staff and process

Twelve of 35 staff members in KemI's Division of Hazard and Risk Assessment work full time evaluating pesticide re-registration data as well as new registrations, and preparing written reviews. Of the 12, three are toxicologists, responsible for reviewing toxicology data, and nine are ecotoxicologists, responsible for reviewing ecotoxicology data. The reviews of toxicology and ecotoxicology data are done separately. In addition, the division has 2 chemists who review physical chemistry data on pesticides if necessary (i.e. if something appears out of the ordinary). Consultants are also used to produce about 50% of the toxicology reviews and about 20% of the ecotoxicology reviews. Among the consultants used to conduct the reviews, toxicologists come from the Institute of Environmental Medicine, a government institution, or from universities; ecotoxicologists come from universities. Data review staff for re-registration are the same staff who conduct data reviews for registration of new pesticides. KemI's Approval Division is also involved in the registration and re-registration of pesticides.

Number of People (person hours) Involved in Work on Pesticides

		re-registration	new registration
Hazard and Risk Assessment Division	toxicology	2	1,5
	ecotoxicology	8	2
Approval Division		12	11

In general, one scientist (or sometimes a team of two) does the entire toxicology or ecotoxicology evaluation of a pesticide. Staff work independently in conducting their data reviews. However, pesticide review staff interact regularly with KemI staff not working directly on pesticides, and they may also consult with internal and external expert groups established in specific scientific disciplines or on specific issues, e.g. cancer, reproductive toxicology, genotoxicology, allergy, classification/labelling. Outside expert groups are composed of 3-6 university scientists with a staff member from KemI serving as secretary. Internal groups are led by the secretary of the external group. In general, pesticide data review staff will consult first with the internal group and then, if necessary, with the external group, if a specific problem or question arises. The staff member conducting the review determines how much assistance from other staff or expert groups is needed.

KemI believes that its experienced and high-quality staff and contact with the scientific community are its strongest asset in the field of hazard and risk assessment. New staff learn their jobs through an apprenticeship system as well as through general introductory training. Continuing education/training is provided for all staff through monthly seminars with invited speakers, arrangements to work on projects with outside experts, and an environment that encourages staff to develop expertise in specific areas.

In recent years, Sweden has worked with other countries to produce collaborative evaluations (5-10 per year with other Nordic countries) and to share evaluations (with the Netherlands). Sweden notes that the arrangement with the Nordic countries works well because they have agreed on a common structure for the reviews. Evaluations done by other

countries have been useful but generally are used only as background for an independent review done by Sweden.

Quality control

1. Consistency of reviews

KemI has published a report, Principles for Identifying Unacceptable Pesticides (1992), which sets out cut-off criteria for determining when a pesticide would be considered unacceptable from a health and environmental protection standpoint on the basis of its intrinsic properties. These criteria refer only to pesticides used in agriculture and areas of use with similar handling situations, where the exposure of humans and the environment cannot be considered to be very low. The cut-off criteria are meant to facilitate a uniform and efficient handling of pesticide applications. Sweden notes, however, that the report is used as a strong guideline but not as a computer programme: reviewers are expected to use their judgement and to apply the cut-off criteria as grounds for concern but not necessarily for total rejection of the pesticide. (Need for the pesticide might be high or exposure low, for example.) The guidelines are most strictly applied in cancer and reproductive toxicity.

Quality of data reviews is also ensured through use of the expert groups, and through a system of internal review that is required of all pesticide data evaluations. Before they are made final, all evaluations are presented by the reviewer (whether staff member or consultant) to a meeting of senior staff from the Divisions of Hazard and Risk Assessment and Pesticide Approval, who review the documents in detail. Experts at the meeting judge the evaluations against Sweden's established criteria and may challenge the reviewer's conclusions. Data evaluations are also circulated for comment to other staff of the Pesticide Approval Division.

2. Data quality

In principle, Sweden requires that studies in all test disciplines be done in compliance with GLP principles and that study submitters indicate whether GLP was followed. This rule is not rigidly applied, however. Most new studies are done by GLP, but many older studies, as well as those done by universities, are not. In such cases, Sweden judges studies on a case-by-case basis to determine whether they can be used. Sweden notes that one reason why non-GLP studies are not automatically rejected is that such studies can show adverse effects and therefore can still be useful. The GLP requirement is applied more strictly to studies that are used to show safety.

Sweden's data reviews do indicate, but only as a general statement for the whole review, whether or not the original studies complied with GLP. Sweden has not yet developed a formal system for indicating study compliance with GLP.

Sweden generally requires that studies be done according to OECD test guidelines, although studies following other guidelines may also be accepted. Sweden would not have a policy to reject studies following other guidelines, since they might contain important information. The data review reports should always indicate what guidelines were used.

Sweden has a laboratory monitoring programme, carried out by the agency SWEDAC, which tests equipment and which will audit laboratories at the request of KemI (such requests are rare). Sweden also has legal authority to impose penalties or reject a pesticide registration if data are falsified (this occurs rarely). The number of toxicity and ecotoxicity studies performed in Sweden on pesticides is low.

3. Data used/reviewed

Re-registration data reviews are done the same way as new pesticide data reviews. Old studies are not regularly re-reviewed, particularly if a good evaluation of such studies done after 1986 is already available. New studies are always reviewed, and Sweden notes that in the field of ecotoxicology, new studies constitute the majority of the database. As a rule, data in all test areas are reviewed simultaneously; however, if a particular adverse effect is known or suspected, data in that area might be reviewed first, potentially avoiding the need for a full evaluation of the pesticide. In addition to hazard and risk, Sweden considers efficacy and need for the pesticide, as well as availability of other chemical or mechanical methods.

Sweden always requires original data reports and never relies on summaries alone. Sweden has the authority to request raw data, but this is rarely done.

4. Study documentation

Sweden keeps files of all studies reviewed in its Registers of Applications; the pesticide data reviews, which are filed in a separate database (BIBLINE), reference the original studies.

Availability of reports

Sweden's data review reports are published and available.

3.10 SWITZERLAND

Background on re-registration programme

Switzerland does not have a formal re-registration programme; re-registration is accomplished through the same process that is used for new pesticide registration. The legal basis for registration requires a pesticide product to be sufficiently efficacious and to cause no detrimental side effects, if used according to the label, to the health of the applicator or the consumer of the food crops, to the quality of the produce, or to the environment.

The following possible situations may prompt actions to re-evaluate and re-register a pesticide and to modify or withdraw its registration:

- extension of the registered uses to new fields of application (additional crops, pests, different time/mode of application),
- omission or addition of specific uses (e.g. restrictions on use in areas where ground water is protected or where sensitive crops/plants may be harmed),
- new evidence of toxicological or ecotoxicological importance (e.g. allergenic properties or adverse effects on beneficial arthropods) leading to use restriction or even complete withdrawal,
- development of pest resistance (leading either to complete withdrawal or registration of a specific active ingredient only in combination with other active ingredient),
- other adverse side effects (such as off-flavour of the crops, fermentation inhibition etc.),
- appearance of new, more appropriate products,
- recommendations by international organisations, legal actions by other countries, information from the registration holder or from the scientific community.

Switzerland characterises its registration/re-registration process as dynamic and flexible with product efficacy (optimisation of dosage, timing etc.) and safety (toxicity, environmental behaviour etc.) being central and of equal weight in a pesticide evaluation.

Data review staff and process

Re-registration data reviews are done by the same staff that review data for new registrations. Different staff review different types of data, according to their expertise. Most of the data review staff work in the three agricultural research stations that are responsible for field crops, fruit and wine growing, vegetables, ornamentals and industrial weed control. Staff in the agricultural research stations evaluate efficacy, phytotoxicity, ecotoxicity and environmental fate. Health department staff review toxicology data, and a meeting of staff from the health and agriculture departments and from regional governments evaluate residue data.

Switzerland's process for reviewing pesticide data involves several steps.

In the first step, data on agronomy and environmental behaviour are reviewed by staff in the three agricultural research stations which are experimentally engaged in the respective fields of science. At the same time, experts from the health department evaluate the toxicology data, writing a summary review.

In the second step, an expert group of 12-20 people, with representation from the health department, regional offices (responsible for enforcement), and the agriculture department meets three times a year to review toxicology and residue data in order to set tolerances according to good agricultural practices. This group also develops recommendations concerning applicator safety. Another group of experts with representation primarily from the agricultural department (about 40 people) meet once a year in the autumn

to consider the recommendations concerning registration, including conditions of use, pre-harvest intervals, etc.

If neither expert group expresses major concerns, the third step is registration of the pesticide for specified uses under defined conditions.

If major concerns are expressed about a new or old pesticide, registration is limited or denied. In such cases a formal procedure must be followed, which grants certain rights to the registration holder or applicant.

Quality control

1. Consistency of reviews

Switzerland intentionally has no specific trigger values for specific properties because this would prevent compromise. Pesticides are evaluated on a case-by-case basis, with consideration of benefits as well as risks. Consistency in reviews is accomplished through the group discussion process and by virtue of the fact that staff remain in their posts for a long time. Staff receive no specific training, but new staff are trained on the job and, initially, work under the supervision of an experienced worker. New staff are encouraged to contribute new ideas.

2. Data quality

Switzerland prefers that studies comply with GLP but this is not an absolute requirement. Rather, studies are judged on a case-by-case basis. Switzerland notes that compliance with GLP does not ensure that a study is scientifically sound, and that non compliance does not necessarily mean that a study is unsound. In the area of toxicology, however, GLP is increasingly required. Switzerland's data reviews do not indicate whether GLP has been followed.

Switzerland indicates that wherever possible studies should be done according to OECD test guidelines. However, this is not always possible (particularly in cases where an OECD guideline has not yet been developed!); thus studies done by other internationally accepted guidelines -- e.g. U.S. EPA, German BBA, or EPPO -- will be accepted.

Switzerland has a programme for inspecting and auditing laboratories, which is run jointly by the health and environment departments. However, it is up to the individual data reviewer to request an investigation. Fines for falsifying data can be issued under the normal penalty system for fraud.

3. Data used/reviewed

Data review of a pesticide is generally at least a one-year process and, in most cases, is accompanied by experimentation in critical topics. There is no difference in registration and re-registration reviews except that, for old chemicals, experience from past use is considered. All available data are included in the review; these data are provided by

the applicant (for new compounds) and/or are known from scientific literature (re-registration). Switzerland relies on data summaries as compiled by the applicant or international organisations (FAO, WHO, CCPR, IARC, ECETOX, CIPAC, EPPO, OILB, OECD, etc.) but, on a case-by-case basis, may consider more detailed information such as that contained in the original reports.

4. Study documentation

Switzerland does not have a tracking system for studies reviewed, but does keep the studies filed in stacks in a library. Protocols of the expert group meetings are filed as well as the summary reports of the individual experts.

Availability of reports

Protocols of the expert group meetings as well as summary reports by individual experts are kept confidential. However, the results of the committee-discussions are published (registrations, tolerances, etc.)

3.11 UNITED KINGDOM

Background on re-registration programme

The U.K. began a programme to review and re-register pesticides in 1986 under the Control of Pesticides Regulations (issued under the 1985 Food and Environment Protection Act). Previous to this, pesticides were dealt with under a voluntary agreement between industry and government called the Pesticide Safety Precautions Scheme. When the COPR came into force, all those active ingredients in pesticide products which were already cleared under the previous scheme were given approval pending review.

The pesticide re-registration programme does not require registrants to re-apply for their approvals. Rather, it identifies gaps and inadequacies in the old databases and sets deadlines for registrants to submit new data to fill these gaps. The results of the data reviews are imposed on the existing approvals. Separate re-registration projects were initiated for agricultural and non-agricultural pesticides: re-registration of agricultural pesticides was undertaken by the Ministry of Agriculture, Fisheries and Food (Pesticide Safety Directorate, or PSD); re-registration of non-agricultural pesticides was undertaken by the Department of Employment (Health and Safety Executive, or HSE).

Pesticide Safety Directorate -- review of agricultural pesticides

Priorities for re-registration of agricultural pesticides come from: (1) a Priority List for the review of established active ingredients, established in 1990 and based on the data of original registration, total area treated by the pesticide, likelihood of operator exposure, and other specific concerns, such as water contamination, identified by government departments; and (2) any adverse findings which point to immediate concerns. Reviews for the Priority List

deal with all safety aspects; ad-hoc "emergency reviews" deal only with the specific issues raised.

There are several differences between re-registration and registration data reviews. Re-registration reviews:

- are done according to a schedule determined by PSD, rather than chronologically, as for new registration applications;
- may include data from all registrants as well as interested parties such as growers, trade associations, and consumer groups;
- include a literature search which supplements the raw data supplied by companies, especially in the wildlife and environmental areas where data is often sparse for old compounds;
- generally do not include an assessment of efficacy or availability of alternatives, unless it appears that the product(s) may be banned or severely restricted;
- consider all products containing the relevant established ingredient;
- result in recommendations that are circulated for comment to data holders/registrations before they are made final;
- take much longer than new registration reviews, because of data protection issues and the review/comment phase.

Re-registration reviews include all available data, both those previously submitted to support the original registration and those sent in for the re-review. Data in different test areas are generally evaluated simultaneously; however, if areas of serious concern are identified during the course of the evaluation, e.g. chronic toxicity studies, assessment of other less contentious parts of the data package could be postponed until the serious concern is resolved.

Health and Safety Executive -- review of non-agricultural pesticides

The review programme for non-agricultural pesticides covers active ingredients registered before 31st December 1980, together with those used in antifouling products. The review process is divided into two phases: (1) an "initial review" of data summaries and prioritization of active ingredients for further review, based on data quality and initial risk findings; and (2) "further review" of the full reports of studies which were previously summarized as well as information obtained through a literature search; this includes a risk assessment of each product and peer review of the risk assessment by the Registration Authority.

NOTE: The rest of this description covers only activities of the Pesticide Safety Directorate.

Data review staff and process

Review of data for registration and re-registration of agricultural pesticides is done by staff in the Specialist Branches, one of three types of branches that comprise the PSD. There are Specialist Branches in toxicology (11 staff members), ecotoxicology (7), residues (6), and efficacy (19). The Specialist Branches review data at the request of the two Commissioning Branches which are responsible, respectively, for the registration of new substances and the re-registration of existing ones. The third branch of the PSD is the Policy Branch.

Staff in both the Specialist and the Commissioning Branches are actively involved in the data review process. One staff member, a "Specialist Author," in each Specialist Branch is assigned to conduct the initial review of the data in the relevant test area and to write a first draft of his evaluation. This initial review involves numerous informal meetings within the Specialist Branch, and culminates in a formal Branch meeting to consider the first draft of the evaluation. When the individual Specialist Branches have agreed on their first drafts, the combined evaluations are submitted for peer review by a meeting of all the Specialist Authors and the co-ordinator for that pesticide from the Commissioning Branch, who is called the Co-ordinating Author. The meeting considers the data package as a whole and identifies the most important aspects of safety and efficacy.

New staff in the PSD receive an introductory "package," but the majority of training is informal and in-house, and consists mainly of continual assessment of more junior staff by line managers. It is always possible for staff to take up training, including pursuit of higher degrees in specific areas, outside the Directorate at universities and colleges.

Quality control

1. Consistency of reviews

Consistency among data reviews done by different reviewers is ensured both by the peer review process and by the use of in-house and international standards. PSD has established a number of in-house "standards" and guidance notes for assessing the hazard of pesticides. These documents often contain trigger values and other indicators for risk assessment; the trigger values, however, are not regarded as absolute values to be strictly applied. Data reviewers are expected to use expert judgment in applying the values in the various risk assessment schemes. PSD is also making increasing use of international standards as these become validated and agreed: examples are the COE/EPPO risk assessment scheme for non-target species and the UNEP/FAO/WHO guidelines on dietary intake.

2. Data quality

PSD’s current policy requires all mammalian toxicity studies started after 30 June 1988, and all physico-chemical, ecotoxicological, and other safety studies started after 1 January 1993 to be GLP-compliant. Efficacy data are not required to be GLP-compliant. (It should be noted that PSD’s GLP policy may change in some respects in order to harmonize with the EC Review Programme.) PSD requires data submitters to indicate, on a standard form, relevant details of the studies including whether the studies were carried out in

accordance with GLP. The acceptability and significance of non-GLP studies is determined on a case-by-case basis: PSD does not automatically request new studies, generated in accordance with GLP, if the existing data are collectively satisfactory. The review reports do not necessarily indicate whether individual studies are GLP-compliant, although this is taken into account when assessing the validity of the studies.

In the U.K., the monitoring of laboratories and facilities for GLP compliance is carried out by an advisory unit at the Department of Health on behalf of all other departments. Monitoring is done both on a cyclical basis (general inspection of all facilities) and in individual study audits, usually done at the request of one of the regulatory authorities on the basis of some concern. A list of "verified" facilities is published annually. Under the Food and Environment Protection Act 1985 and the Control of Pesticide Regulations 1986, U.K. Ministries can issue fines for falsifying or withholding data.

3. Data coverage

PSD reviews both company data and published data, but does not accept summary reports. It is taken into account that published papers may not have the scientific validity of modern data, carried out to GLP standards. Specialists have the authority to request raw data, slides etc.; this does not occur routinely, but examples where it may occur include requesting re-reading of slides by an independent pathologist and preparation of new photographs of existing slides.

4. Study documentation

Computerized and hard copy lists are kept of all the data/information included in a data review. Maintenance of these lists is the responsibility of the Co-ordinating Author. The importance attached to each study with respect to the conclusions reached is clearly indicated in the review reports.

Availability of reports

Under U.K. legislation, information held in support of pesticide approval applications can be made publicly available. Both the supporting data (studies) and the PSD's evaluation documents are therefore available under certain conditions.

Members of the public or organisations can obtain copies of evaluation documents by submitting a written request and a nominal fee. Standing orders for documents can also be arranged on request. Recipients of these documents are advised that the documents may not be put to commercial use, that no part of them may be published (without written permission of the government) or distributed, and that breach of these conditions is a criminal offense.

If having read an evaluation document an enquirer wishes to follow this up, an application can be made to access the supporting data held by the regulatory authority. The request must be justified and if granted the information may only be studied on the premises of the regulatory authority: notes may be made but the data cannot be copied or removed. Only commercially confidential information such as formulation and manufacturing details may

be excluded, as can individual medical details or addresses of laboratories and names of personnel.

The PSD also publishes an annual report which includes information on reviews undertaken and the overall conclusions reached.

3.12 UNITED STATES

Background on re-registration programme

Pesticide re-registration in the U.S. is done by the Environmental Protection Agency (EPA). The re-registration programme covers all pesticides with products first registered before November 1984. EPA's efforts to call in data on old pesticides date back to 1972. The current programme, however, is covered by a 1988 law which mandates that the bulk of pesticide re-registration be completed by 1997. In response to this law and the new resources provided to implement it, EPA expanded and re-organised its re-registration programme in the late 1980s. EPA now estimates that the 1997 deadline will not be met for a significant portion of the active ingredients undergoing re-registration. This is due to various factors in the review process, most notably the time needed for registrants to complete required studies and for EPA review of those studies, as well as the receipt of studies judged to be unacceptable. Currently, 405 re-registration cases, comprising approximately 650 active ingredients, are being supported for re-registration. EPA has issued Re-registration Eligibility Documents, describing the products eligible for re-registration, for 47 cases covering 72 actives.

Re-registration data reviews are, in large part, done by the same staff and in the same manner as new registration reviews. The principal difference concerns the data requirements. EPA's data requirements for new registrations continue to evolve in line with scientific developments such as the availability of new test methods and new risk concerns. By contrast, the requirements for re-registration were fixed at a certain date, so as to avoid the confusion of a moving target. For both registration and re-registration reviews, EPA considers efficacy only for public health pesticides. Benefit information is not normally developed for re-registration decisions, except in cases where the hazard is sufficiently high to warrant regulatory restrictions.

Data review staff and process

Data review and re-registration involves a considerable amount of teamwork and co-ordination in EPA's Office of Pesticide Programs (OPP). The scientific staff who evaluate the original data submissions and write the review reports reside in two OPP Divisions: Health Effects, and Environmental Fate and Effects. Staff in other OPP Divisions provide information on use, exposure, and biological and economic impacts. Chemical Review Managers in the Special Review and Re-registration Division co-ordinate the process, including drafting the Re-registration Eligibility Documents which summarize key findings regarding hazard and risk (REDs are regulatory decision documents which constitute the final step in evaluating the active ingredient before actual re-registration of the products).

Completing a scientific review involves several steps and participation of multiple staff. The process begins with the staff scientists, who are organised by discipline and who either evaluate individual studies in that discipline or review the work of contractors who have evaluated the studies. These data reviews of individual studies are then reviewed by supervisors in the science divisions, and often by internal OPP science branch peer review groups. Once all the reviews have been completed in a broad test area (e.g. mutagenicity), a lead reviewer is named to assemble the individual data reviews and identify those studies that are core (meet all GLP requirements and have significant results) and those that are supplemental (do not meet the "core" criteria but may be used to corroborate core study findings). The lead reviewer then evaluates the results using weight-of-evidence, "core" ratings, and recommendations from the individual reviews; he presents his findings in a summary report that becomes part of the science chapter for the RED. This summary report will have been subject to review by the science divisions' "co-ordination staff" who provide quality control and ensure that science decisions are consistent with program policy. Each scientific branch has also established its own procedures for introductory and continued training. Beginning staff in OPP normally operate under the supervision of senior scientific staff.

In fiscal year 1992, OPP allocated 158 "work years" to the re-registration effort, including:

- 33 in the principal regulatory division for re-registration, Special Review & Re-registration Division (SRRD staff co-ordinate the re-registration process and draft the REDs);
- 100 in the two science divisions: 59 in the Health Effects Division and 41 in the Environmental Fate and Effects Division;
- 13 in the Registration Division (RD staff carry out the administrative process of re-registering individual products);
- 12 in the Biological and Economic Analysis Division.

Through September 1993, EPA made initial re-registration eligibility decisions for 47 cases covering 72 actives, issued 376 comprehensive data call-in letters, and reviewed over 9,100 studies, excluding Product Chemistry studies, that relate to actual or pending re-registration decisions.

Quality control

1. Consistency of reviews

The overall quality of OPP data reviews is ensured by the system of supervisory and peer review within each scientific branch. To help ensure consistency of the reviews, OPP has developed Standard Evaluation Procedures which provide guidance on how to conduct data reviews in each test area. These procedures provide a standard format for the documents and indicate levels of concern for labelling, tier testing, and other regulatory decision-making. In most test areas the procedures do not set rigid triggers or hazard levels, leaving this to the risk management process.

For the most part, OPP has flexibility in applying levels of risk concern; in fact, OPP is directed by federal law to balance risks and benefits in regulating pesticides. However, OPP regulations do set rigid levels for acute toxicity for labelling and use restrictions. In addition, U.S. safety law prohibits residues of carcinogenic pesticides in food.

2. Data quality

EPA regulations require GLP for all studies initiated after mid-October 1989. Study submitters must include a statement indicating the study's compliance with, or any deviations from, GLP. Non-GLP studies may be considered in OPP data reviews as supplemental information and, in the absence of other data, may be significant in regulatory decisions. OPP data reviews do indicate whether or not individual studies complied with GLP.

EPA has an ongoing laboratory inspection programme for compliance with GLP. All testing facilities conducting GLP studies must permit EPA or U.S. Food and Drug Administration staff to inspect the facility for GLP compliance. Civil penalties (fines up to $5,000) or criminal penalties (fines up to $50,000 or imprisonment for up to 1 year) may be issued against any pesticide registrant who knowingly violates any provision of OPP's statute or regulations.

EPA requires that studies submitted to support a pesticide registration be carried out in accordance with EPA or OECD test guidelines (although EPA warns that care should be taken with tests for which OECD guidelines deviate from EPA's).

3. Data used/reviewed

OPP re-examines all old studies to support a pesticide registration and, if they are found acceptable, does not require them to be replaced. OPP does not review summaries but requires original study reports with detailed tabulations of the experimental data, including individual animal data tables. These serve as the basis for OPP to do a comprehensive statistical review of the data. Reviewers may request submission of raw data if necessary.

Because OPP does not have adequate resources to review all re-registration studies as soon as they are submitted, the following priorities have been set:

Highest priority

- studies showing adverse effects
- studies pertaining to pesticides scheduled for a re-registration decision in the current year
- studies that could trigger higher tier data requirements
- toxicological studies (chronic, oncogenic, reproductive, teratogenic)

Second priority

- studies pertaining to pesticides scheduled for decisions the following year
- studies from disciplines with historically high rejection rates

Third priority

- other studies.

Studies are quickly screened to determine relative priorities. Lower priority studies may await review for several years.

4. Study documentation

OPP uses several systems for documenting and keeping track of reviewed studies. All studies received by OPP are immediately listed in a general database (the Pesticide Document Management System) after screening to ensure basic formatting requirements are met. Guideline and study information on re-registration are also entered into the re-registration data base (Chemical Review Management System) used by the Special Review and Re-registration Division chemical review managers. Study assignments (i.e. scientific reviewers and chemical review managers) are recorded in the Pesticide Regulatory Action Tracking System with review due dates.

Availability of reports

OPP data review reports are publicly available and are not subject to confidential treatment procedures or foreign disclosure requirements. OPP routinely screens its reports prior to release to ensure that they contain no confidential information, but there is a presumption of relatively unrestricted sharing of the reports.

3.13 JOINT FAO/WHO MEETING ON PESTICIDE RESIDUES

Background on data review programme

Joint Meetings of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues, usually known as the Joint FAO/WHO Meeting on Pesticide Residues or JMPR, have been held yearly since 1963. The JMPR estimates, through these two expert groups, the level at which pesticides widely used in agriculture can be safely tolerated by the human body. Thus far, more than 200 pesticides have been evaluated. The evaluation ends with publication of a monograph summarizing the data reviewed and recommending food "tolerance" levels. The recommended levels are used by national regulatory agencies and by the Codex Alimentarius Commission to establish acceptable levels of pesticides in foodstuffs.

The FAO Panel of Experts is responsible for reviewing pesticide use patterns including good agricultural practices, data on the pesticide chemistry and composition, and methods for analysing pesticide residues and estimating maximum residue limits (MRLs) on food commodities. The Panel reviews new compounds as well as re-evaluating older compounds with the aim of preparing a detailed evaluation or monograph which is then published and distributed widely. The WHO Expert Group is responsible for reviewing toxicology data and for estimating acceptable daily intakes (ADIs).

Most priorities for JMPR review are determined by the Codex Committee on Pesticide Residues (CCPR). In addition, if a country identifies a safety problem, the JMPR will review the pesticide at its request.

The original structure of the review process was based on compounds for which the ADI was established more than 10 years ago. It was agreed at the 25th Session of the CCPR (April 1993) that the primary criterion for initiating a periodic review would be that the compound had first been reviewed more than 10 years ago. It is recognized that there is a need to discuss modifying the prioritization scheme so as to include other criteria such as dietary intake and the pesticide review schedules of member countries.

Data review staff and process

FAO Panel of Experts

The FAO Panel of Experts is composed of six to eight individuals, primarily from academia and national governments, who serve on the Panel as experts in their own right and not as representatives of a national government. They are selected on the basis of their experience in all areas of pesticide residue chemistry.

Each Panel member considers all of the available data for the compounds for which he is responsible. Panel experts also exchange information with the WHO Panel of Experts on Pesticide Residues where there are concerns about the toxicological significance of actual residues (i.e. residues at harvest). Information on plant and animal metabolism, animal feeding studies, field trials, and information on aspects of environmental fate (e.g. soil metabolism) are considered in the review process.

While no training for the FAO process is provided, new Panel members are given a single "straight-forward" compound to evaluate and are generally paired with a more experienced Panel member who also evaluates the data. New members participate fully in the Panel deliberations.

WHO Expert Group

The WHO Expert Group consists of eight to ten scientists from various governments, called Temporary Advisers. As with the FAO Panel, these individuals serve on the Expert Group as experts in their own right and not as representatives of a national government.

Each scientist reviews all the data on a particular pesticide and prepares a "working paper" that summaries and comments on these data. In most cases, the Temporary Advisers are able to use information from reviews that have already been performed at the national level. The working papers are submitted to a WHO Member assigned as the peer reviewer, who makes further comments and proposes action to be taken. Temporary Advisers and Members are encouraged to work together during the preparation of the working papers.

Quality control

FAO Panel of Experts

1. Consistency of reviews

At present, no specific triggers or hazard levels have been established for use by the FAO Panel. However, the exchange of reviews and discussion of individual compounds in the course of the Panel meeting ensures a considerable amount of consistency in the review process. A guideline on the operation of the FAO Panel, whose objective is to produce greater consistency, is under preparation.

2. Data quality

The data submitted in support of a maximum residue level are wide ranging and include information on physical-chemical properties, plant and animal metabolism, analytical methods, and residues. In general the FAO Panel has no requirement that studies follow specific protocols, and its data reviews do not indicate which protocol was used. However, FAO notes that laboratory data are generally conducted according to internationally accepted test protocols (e.g. ISO, CIPAC, AOAC, ASTM), as they are used to support registrations in different countries.

In the area of field testing (e.g. residue trials), guidelines available at the international level are by necessity general in nature. At the national level there are differences in the specific elements or level of detail included in study reports. These reports usually do not reference the "guideline" used. FAO notes that residue data developed for national regulatory authorities in developed countries is usually generated in accordance with GLP principles. The FAO Panel determines the acceptability of the individual data sets on a case-by-case basis.

The Panel considers individual studies in the context of the available data, what is known of compounds of similar chemistry, etc. Studies of questionable reliability are not included in the final evaluation. The Panel determines on a case-by-case basis how much weight will be assigned to each study in arriving at a final decision.

3. Data used/reviewed

In order for a compound to be accepted for re-evaluation by the FAO panel it must be supported by a complete data base. Data summaries are not accepted; only detailed reports are considered. Where there are questions about individual study reports, the Panel member may contact the data submitter for clarification or further information. The order in which the data are reviewed has to this point been left to the discretion of the individual experts.

At present the Panel is likely to review old studies as well as new ones, particularly in those instances where detailed results of the original review are not accessible and modern replacements are not available. It is often the case, however, that the usefulness of older

studies is limited as they may be inadequately reported. Decisions regarding the inclusion of older studies are largely taken on a case-by-case basis.

4. Study documentation

A central file of the studies submitted for review has recently been established. The published monographs list the references used in evaluating the pesticide.

Availability of reports

The deliberations of the FAO Panel of the JMPR are available in two formats. The Report of the Meeting contains the overall conclusions of the review and the recommended maximum residue levels. The Report is supplemented by the Evaluations which consist of detailed reviews or monographs of the data submitted in support of the recommended maximum residue level. Both documents are distributed to contact points in all Member countries of the FAO, as well as universities, libraries, and FAO Regional offices.

WHO Expert Group

1. Consistency of reviews

WHO does not apply specific triggers or hazard levels, but relies on its members for judgments and decisions regarding acceptable/unacceptable hazard. WHO depends upon a reasonably stable membership to provide consistency.

2. Data quality

WHO encourages compliance with GLP principles but does not require it. WHO notes that it is obvious from the full study reports whether each individual study was done according to GLP. Treatment of studies not done according to GLP is determined on an *ad hoc* basis. WHO reviews do not indicate whether or not studies complied with GLP, but deficiencies, particularly in newer studies, are noted. WHO is not involved in laboratory monitoring for GLP.

3. Data used/reviewed

Because of the nature of the WHO reviews, i.e. limited to residues in food, oral studies are generally considered most relevant; benefits and efficacy are not addressed. All available data in the appropriate areas are reviewed including old studies, which are compared with newer ones to see if the results are consistent. WHO requires full study reports, but Temporary Advisers also depend upon reviews done at the national level to identify problems/key areas for attention. Tissue slides have been requested in rare cases. Data in all areas are reviewed simultaneously.

4. Study documentation

The comment and evaluation sections of the evaluation reports usually identify those studies which served as the basis for decision-making (establishment of the MRL).

Availability of reports

WHO publishes summaries of all studies reviewed (toxicology evaluations).