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REPORT OF THE PILOT EXERCISE ON CLASSIFICATIONS FOR SELECTED CHEMICALS ASSESSED AT COCAM

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FOREWORD

This document reports the results of a pilot exercise to suggest classifications according to the Globally Harmonised System for a number of chemicals assessed in the OECD Cooperative Chemicals Assessment Programme (CoCAP). The exercise was carried out in two phases at Cooperative Chemicals Assessment Meetings (CoCAM) 4 and 5 (16 – 18 April and 15 – 17 October 2013, respectively), with eight member countries and BIAC taking part overall in the two phases. Three chemicals for which assessments had been agreed at CoCAM 3 were selected for the first phase of the exercise. Classifications were submitted for all endpoints for these chemicals. The second phase included classification suggestions for all endpoints for another chemical that had been agreed within the CoCAP as well as a reinvestigation of selected endpoints for two chemicals from the first phase.

The aims of this exercise were to i) gain insight into the possible reasons for differences in classifications that had been proposed in different regions for the chemicals selected for the first phase; ii) explore how useful the conclusions reached in OECD SIDS assessments are for classification purposes; and iii) see whether there is scope to improve the programme's outputs or increase the SIDS assessment documents' utility for classification purposes.

The Joint Meeting agreed to the declassification of this report on 19 September 2014. This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

Contents

Background

1. In March 2010 the OECD published a report entitled "Classification and Labelling of Chemicals According to the UN Globally Harmonized System: Outcome of the Analysis of Classification of Selected Chemicals Listed in Annex III of the Rotterdam Convention" (ENV/JM/MONO(2010)7)[1].

2. The 2010 publication reported the results of an exercise conducted within the OECD Cooperative Chemicals Assessment Programme in which experts from seven member countries reviewed available classifications for four chemicals in Annex III of the Rotterdam Convention. Additionally, a further member country submitted observations on the classifications based on their national reviews of the underlying study data. Available classifications were those from the EU, Japan and New Zealand, and the four chemicals were lindane (with classifications for seven hazard classes), methamidophos (with classifications for five hazard classes), methyl parathion (with classifications for seven hazard classes) and thioersal (with classifications for 11 hazard classes).

3. The 2010 publication noted differences in classifications from the three classification sources for many of the endpoints (classes) that were reviewed. The report concluded that the main reason for these divergences was because different datasets had been used, but also that issues around data interpretation and application of the classification criteria themselves contributed to the differences. Other specific issues identified included validity/reliability of the data, use of secondary or non-standard test data, different uses of read-across (for example in the EU a "group entry" has been made for a series of mercury-containing organic chemicals), and terminology within OECD test guidelines (e.g. "slightly" versus "mildly" irritating). The experts involved in the review concluded that about seven endpoints for which different classifications existed should not be too difficult to resolve, but there still remained many that were likely to prove more difficult to resolve. (NOTE: It was not the intention of this report to propose any changes in classifications to the bodies responsible for the available classifications. The exercise was aimed purely at gaining insights into why classifications could differ and at furthering stakeholders' awareness of the issues).

4. Following on from the 2010 report, at its 5th meeting the OECD Task Force on Hazard Assessment (TFHA) suggested that OECD perform a pilot exercise on a selection of chemical assessments agreed at the third Cooperative Chemicals Assessment Meeting (CoCAM 3), held in October 2012, to make an informal proposal for their classification. The Task Force recommended that the focus of this exercise should be on those chemicals with available classifications in countries or regions that diverged to i) gain further insight into the reasons for the differences and ways in which they might be overcome and ii) explore how useful the conclusions reached in the SIAP are for classification purposes, and whether there is scope to improve the programme's outputs or increase their utility.

[1] Available at: http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/JM/MONO(2010)7&doclanguage=en

Introduction and Overview

5. The secretariat obtained classification information using eChemPortal from Classification and Labelling inventories in the EU[2], Japan[3] and New Zealand[4] for all substances to be discussed at CoCAM 3. Substances that were selected for the classification exercise were as follows, based on a lack of harmonised classification and a high number of diverging classifications. The SIDS Assessments for these substances are available through the OECD Existing Chemicals Database (see References section).

- • 2,4-Dimethyl aniline, CAS 95-68-1 (a member of the SIDS category assessment Dimethylanilines, which includes all 6 possible substitution patterns; 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethyl aniline);

- • Nonane, CAS 111-84-2 (a member of the SIDS category assessment C9-C14 Aliphatic Hydrocarbon Solvents, which includes linear chain, iso-parrafins and some complex hydrocarbons)

- • Disodium ethylenediaminetetraacetate, CAS 139-33-3 (2Na EDTA; a member of the SIDS category assessment Amino Carboxylic Acid-Based Chelants, which includes various EDTA and HEDTA salts)

- • Titanium dioxide, CAS 13463-67-7 (subsequently omitted as the assessment was not agreed at CoCAM 3)

6. The Netherlands (NL), Switzerland (CH), Italy (IT), Russia (RO), Japan (JP; environment only) and BIAC (JCIA) offered to take part in the exercise. They developed draft classifications with explanations for submission prior to CoCAM 4 (held in April 2013), where the proposals would be discussed. In addition the Netherlands submitted a series of observations on the exercise, culminating in a number of questions that the experts felt most important to answer.

7. At CoCAM 4 it was apparent that significant differences in the member country classification proposals existed for the three chemicals, and it proved not possible to agree on all endpoints for any one chemical (although there were a significant number of endpoints for which there was consensus). There was also discussion on whether the way data are reported in the SIAP and other SIDS assessment documents needs to change for the more complex endpoints (for example, in which SIDS documents scoring details are reported for endpoints like skin corrosion/irritation).

8. As a result, it was suggested to continue the exercise to CoCAM 5 (held in October 2013) to further explore selected endpoints (see below) from the three chemicals and to propose classification for a "less ambitious" case (i.e. a data-rich, single-chemical assessment) already agreed at CoCAM to see how easy reaching consensus would be. Unambiguous instructions on how to go about the exercise were given to participants so that they would follow the same approach when making their proposals for this second phase of the exercise (see Annex 1). This step was taken because participating countries took different

[2] The C and L inventory database (http://echa.europa.eu/information-on-chemicals/cl-inventory) is hosted by the European Chemicals Agency and includes EU harmonised classifications as well as classifications "notified" by chemical producers. In the EU, classifications must be notified to ECHA by suppliers for all chemicals supplied in quantities of one tonne per annum or greater.

[3] Classifications used in Japan according to GHS are available at http://www.safe.nite.go.jp/english/ghs_index.html

[4] Classifications used in New Zealand are available through the Chemical Classification and Information Database (CCID), hosted by the New Zealnd EPA: http://www.epa.govt.nz/search-databases/pages/hsno-ccid.aspx

approaches in terms of the level of detail they went into for the first part of the exercise (i.e. which SIDS assessment document they consulted), and some countries used non-SIDS documents to propose classification. For CoCAM 5, participants were asked to first consult the SIAP, and if it proved unsuitable for classification, to consult the SIAR and finally, if needed, the dossier (participants were also asked to report which assessment document was needed for each endpoint). At its 6th meeting, the TFHA endorsed the continuation of the exercise into a second phase.

9. 2-Vinylpyridine, CAS 100-69-6 (single-substance assessment agreed at CoCAM 2, April 2012), was selected as the data-rich substance from a single-chemical assessment to attempt classification for SIDS and other "common" endpoints according to the GHS at CoCAM 5.

10. For those chemicals already discussed in the exercise, 2,4-dimethylaniline (CAS 95-68-1) was selected to revisit the following human health endpoints at CoCAM 5:

- Acute toxicity, oral route (to explore differences in approach, as suggested by the Russian Federation)

- Carcinogenicity (to explore use of read across and how (analogue) data reporting could be improved in the dossier/SIAR)

- Specific Target Organ Toxicity, Repeat Exposure (to explore differences in interpretation of the key study and the potential for read across/use of supporting data)

and nonane (CAS 111-84-2) for:

- Skin sensitization (to explore use of read across and how (analogue) data reporting could be improved in the dossier/SIAR)

For the environment, 2,4-dimethylaniline was selected to revisit:

- Chronic aquatic toxicity (to explore use of read across and allow Member Countries to express their opinion on how analogue data should be used in the context of the "surrogate system" vs. "direct" use of chronic toxicity data)

11. Three of the original participants took part in this second phase of the exercise. These were the Netherlands, Switzerland (Human Health only) and the Russian Federation. They were joined by Denmark (DK), France (FR) and Japan (JP; HH only), again giving six participants in total. This meant that direct comparisons between the two phases of the exercise were only possible for three participants.

Results of the Exercise and Discussion

12. Results are presented below chemical-by-chemical rather than by exercise phase to make comparison of proposals for relevant endpoints easier. In the case of 2,4-dimethylaniline and nonane results for all endpoints from the first phase at CoCAM 4 are presented first followed by results for the selected endpoints discussed in the second phase at CoCAM 5 (see paragraph 10). Results for these endpoints are structured this way so as not to over-complicate the analysis and because proposals were made by different participants in the second phase of the exercise (direct comparison of classifications with the first phase of the exercise is only possible for three out of six participants). A brief discussion is included after a tabular summary of the results for each endpoint with significant divergence in proposals. This discussion forms the basis for the report's overall Conclusions section. All classification proposals from participants for both phases of the exercise are available in Annex 3.

2,4-Dimethylaniline (CAS 95-68-1)

13. Table 1 displays the classifications that are available in OECD member countries for 2,4-dimethylaniline for endpoints commonly reported in a SIDS assessment. These are given for information only; the basis and rationale for these classifications is not reported, so any differences that are apparent cannot be explored here.

Table 1: Classifications available for 2,4-Dimethylaniline in the EU, Japan and New Zealand

Endpoint	EU C and L Inventory[1]	GHS-J	HSNO CCID[2]
Aspiration toxicity	not classified (9/9)	not classified	not classified
Skin irritation	not classified	not classified	not classified
Skin sensitisation	not classified (9/9)	not classified	not classified
Reproductive Toxicity	not classified (9/9)	not classified	not classified
Aquatic Acute Classification	not used	Cat 2	not classified
Acute Toxicity	3 (o, d, i) 7/9	Cat 4 (o, i)	6.1B (o, d, i) (Cat. 2)
Eye Irritation	not classified (7/9)	Cat. 2	not classified
Mutagenicity	not classified (8/9)	not classified	not classified
Carcinogenicity	not classified (9/9)	not classified	not classified
STOT SE	not classified (9/9)	Cat. 1b	not classified
STOT RE	Cat. 2 (9/9)	Cat. 1b	6.9B (o) (Cat. 2)
Aquatic Chronic Classification	Cat. 2 (9/9)[3]	Cat. 2	9.1B (Cat. 2)

Notes:
Endpoints ordered as per Table 2 for ease of comparison.
[1] the ECHA classification database had nine aggregated entries for the substance, representing 93 notifiers, at the time of searching for this exercise (end November 2012). The classifications reported in the table refer to those most commonly reported for each endpoint by entry, with the number in brackets showing the number of entries with this classification out of the total of nine.
[2] Classifications in New Zealand are categorised according to HSNO Hazard Classes; the GHS equivalent is included in brackets (according to http://www.epa.govt.nz/publications/hsnogen-ghs-nz-hazard.pdf)
[3] The classification notifications for aquatic chronic in the EU were made before the 2nd ATP (adaptation to technical progress) to the EU CLP Regulation (classification, labelling and packaging) was made following the 3rd revision to the GHS in 2009, so can only be based on the "surrogate" system (the basis for the classifications in Japan and New Zealand are likely to be the same).

First Phase: CoCAM 4

14. A summary of the classifications received in phase one of the exercise (CoCAM 4) from the Netherlands, Switzerland, Italy, Russia, Japan (environment only) and BIAC (JCIA) is given below in table 2. Endpoints for which there was broad consensus (in both the proposal and its basis) are listed in "part 1" and endpoints for which classification proposals diverged significantly are given in "part 2". Under each classification proposal (or proposal for no classification) a summary of its basis is given. The reasons for these differences are explored in the paragraphs below the table, endpoint-by-endpoint.

Table 2: Classification Proposals for 2,4-Dimethylaniline (CAS 95-68-1) in Phase One of the Exercise (CoCAM 4)

Part 1: Endpoints for which Classification Proposals were the same						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP (ENV only)**
Aspiration toxicity	not classified	not classified	not classified	not classified	not classified	
rationale	no data	no data	no data	no data	no data	
Skin irritation	not classified	not classified	not classified	not classified	not classified	
rationale	data not sufficient	data sufficient	data not sufficient	data not sufficient	data sufficient	
Skin sensitisation	not classified	not classified	not classified	not classified	not classified	
rationale	no data	no data	no data	no data	no data	
Reproductive Toxicity	not classified	not classified	not classified	not classified	not classified	
rationale	no data (read across from 2,6- not valid)	no data	data not sufficient	no data	no data	
Aquatic Acute Classification	**Cat. 2**	**Cat. 2**	**Cat. 2**	**Cat. 2**	**Cat. 2**	**Cat. 2**
rationale	inv EC_{50} 9.9 mg/L	inv EC_{50} 9.9 mg/L	inv EC_{50} 9.9 mg/L	inv EC_{50} 9.9 mg/L	inv EC_{50} 9.9 mg/L	inv EC_{50} 9.9 mg/L
Part 2: Endpoints for which Classification Proposals differed						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP**
Acute Toxicity (o, i, d)[1]	**Cat. 3 (o)**	**Cat. 3 (o) [Cat. 4 (i)]**	**Cat. 3 (o)**	not classified	**Cat. 4 (o, i)**	
rationale	Mouse LD_{50} 250 mg/kg	Mouse LD_{50} (o) [+ rat LC_{50} = 1.53 mg/l (i)]	Mouse LD_{50}	data not sufficient	Rat LD_{50} 470 mg/kg (o); Rat LC_{50} 1530 mg/m^3 (i)	
Eye Irritation	not classified	**Cat. 2b**	not classified	not classified	**Cat. 2**	

rationale	data not sufficient	based on previous classification (non-SIDS); but scores not reported	data not sufficient	data not sufficient	based on previous classification (non-SIDS); but scores not reported	
Mutagenicity	**Cat. 2**	**Cat. 2**	**Cat. 2**	**Cat. 2**	not classified	
rationale	1) +ve comet assay, bacterial reverse mutation assay, chromosomal aberration (but micronucleus assay -ve). 2) Supporting analogue data	1) +ve comet assay, bacterial reverse mutation assay, chromosomal aberration (but micronucleus assay -ve). 2) Supporting analogue data	1) +ve comet assay, bacterial reverse mutation assay, chromosomal aberration (but micronucleus assay -ve). 2) Supporting analogue data	1) +ve comet assay, bacterial reverse mutation assay, chromosomal aberration (but micronucleus assay -ve). 2) Supporting analogue data	data not sufficient (equivocal results)	
Carcinogenicity	not classified	not classified	**Cat. 2**	**Cat. 2**	not classified	
rationale	data not sufficient (but possible/likely based on pulmonary tumors in mice)	data not sufficient (but read across (2,6-analogue) = carc 2)	pulmonary tumours (mice), *in vivo* genotoxicity	pulmonary tumours (mice), *in vivo* genotoxicity	data not sufficient (but possible/likely based on pulmonary tumors in mice)	
STOT SE	not classified	not classified	not classified	not classified	**Cat. 1**	
rationale	data not sufficient	data not sufficient	no data	no data	adverse effects at low concentrations (250 mg/kg bw effects on	

					blood)	
STOT RE rationale	**Cat. 1** OECD 407 (kidney effects at 10mg/kg)	**Cat. 2** OECD 407: 50 mg/kg bw/d (females; decreased hemoglobin)	not classified data not sufficient (but OECD 407 indicates may be Cat. 1)	**Cat. 1** OECD 407 NOAEL 2 mg/kg bw/day (effects on blood, liver and kidneys)	**Cat. 1** OECD 407 20mg/kg effects on kidney and blood	
Aquatic Chronic Classification	**Cat. 1** (cat 2 ("own" data)	**Cat. 1 (M10)**	**Cat. 2**	**Cat. 2**	**Cat. 2**	**Cat. 1**
rationale	**read across**: no rapid deg & NOECs 0.0095, 0.096, 0.03, 0.1 mg/L (3,4-, 2,5-, 3,5-, 2,3-analogues)[2]	**read across**: no rapid deg & NOEC 0.0095 mg/L (3,4-analogue)	surrogate approach (inv EC_{50}) + **read across** no rapid deg	surrogate approach (inv EC_{50}) + **read across** no rapid deg	surrogate approach (inv EC_{50}) + **read across** no rapid deg	**read across**: no rapid deg & NOEC 0.0095 mg/L (3,4-analogue)

Notes:

"data sufficient" means that data relevant for the endpoint were available that could be used for classification purposes; "data not sufficient" means that data relevant for the endpoint were available, but that there was some shortcoming that meant the data could not be used for classification purposes (e.g. unreliable, or for complex endpoints lacking scoring, detail on timing, severity etc); "no data" means no data relevant for the endpoint were available; o = oral, i = inhalation, d = dermal.

[1]Classification proposals for each of the three routes (oral, inhalation, dermal) are included for acute toxicity; where a classification by route is not presented, this means no proposal was made (e.g. no proposals for dermal acute toxicity were made).

[2]BUT 2,6-dimethylaniline NOEC 2.23 mg/L.

15. The focus of this report is on endpoints for which consensus was not reached, but it is worth mentioning that, as shown in part 1 of table 2, although all countries did not classify the chemical for skin sensitisation the basis for this differed for two participants in the exercise (IT and BIAC), where the data were felt to be sufficient for classification purposes.

16. For **acute toxicity** by the **oral** route, a study in mice and rats was available (Vernot et al 1977) that was reported in the SIAP. Mice were more sensitive in this study than rats (LD_{50} values of 250 and 470 mg/kg bw, respectively). Choice of species represents the first issue for this endpoint; three of the five participants used the mice data to classify the substance in category 3, whereas one participant used the rat data for category 4 classification. While the rat is the preferred species for acute oral studies, other species (in a valid test) can be used for classification purposes according to the GHS (see paragraph 3.1.2.3 of the GHS: "*when experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.*"). The remaining participant concluded that the data were not sufficient for classification purposes, and this highlights the second issue for this endpoint: the way the data were presented in the SIAP. The data were reported as supporting information in the SIAP without reference to the study's reliability, hence those participants who used the SIAP in isolation for the exercise would not have known that the study had been judged reliability 4 (unassignable) in the other SIDS documents (although in the revised dossier, which was not available for this exercise, the reliability had been upgrade to 2, reliable with restrictions; this is discussed further below for the second phase of the exercise under the heading *Second phase: CoCAM 5 revisit*).

17. For **acute toxicity** by the **inhalation** route, three participants felt that available data were insufficient for classification. The remaining two participants classified in category 4, based on a 4h LC_{50} of 1.53 mg/l in the rat from a reliability 4 study that was not reported in the SIAP. For **acute toxicity** (**dermal** route), no classifications were suggested (no data).

18. For **eye damage/irritation**, one study was available in the rabbit according to OECD 405 (Hofmann and Weigand 1986). The study was reported in the SIAP, but lacked scoring and severity details in all of the SIDS documents (SIAP, SIAR, and dossier). Additionally, the study was judged reliability 4. Three of the five participants did not classify based on insufficient test data. The remaining two participants classified in category 2 (or 2b) based on a classification suggested in a non-SIDS review.

19. For **Mutagenicity**, a number of *in vitro* and *in vivo* assays exist that are either valid (reliability 2) or have unassignable validity (reliability 4) with positive and negative findings. In a valid Ames test (OECD 471), the substance was positive with activation and negative without (NITE 2002); five additional studies (reliability 4) gave the same result (CCR 1991, Chung et al 1981, Kimmel et al 1986, Nohmi et al 1984 and Zeiger et al 1988). One reliability 4 Ames test gave a "weakly positive" result (Zimmer et al 1980), whilst one further reliability 4 study gave a negative result (Hartman et al 1979). In a reliable chromosomal aberration assay (OECD 473), the substance was positive with and without activation (NITE 2002); a reliability 4 study gave the same result (CCR 1991). Three reliability 2 *in vivo* assays were available: two comet assays with positive findings (Przybojewska 1999 and Hayashi et al 2000), and one micronucleus assay with negative findings (Hayashi et al 2000). Based on the available data, the SIAP concluded "*In summary, the results from the available studies suggested that members of dimethylaniline category are mutagenic in vitro and in vivo.*" Four of the five participants used a "weight of evidence" approach, using the available data for the substance but in addition supporting data from analogue substances in the dimethylanilines category, to classify into category 2. The remaining participant again followed a weight of evidence approach, deciding that overall the data were equivocal so classification was not possible.

20. The issues of weight of evidence and expert judgement are explored in the introductory text to the GHS. The GHS states (*Weight of Evidence*, paragraph 1.3.2.4.9.5) "*both positive and negative results are assembled together in the weight of evidence determination. However, a single positive study performed according to good scientific principles…may justify classification*", but also says (*Expert Judgement*, paragraph 1.3.2.4.8) "*Expert judgement may also be required in interpreting data for hazard classification of substances, especially where weight of evidence determinations are needed*". The likelihood of variability in underlying datasets (the fact that no two WoE cases for different chemicals for the same endpoint are likely to be the same) suggests that further general guidance on WoE approaches may be needed.

21. For **carcinogenicity**, the SIAP reported a valid study for the analogue 2,6-dimethylaniline indicating carcinogenic responses in mice. As supporting evidence, the SIAP also reported a study with 2,4-dimethylaniline in mice ("*Another carcinogenicity study demonstrated that 2,4-dimethylaniline induced pulmonary tumours in female mice*…"). However, this study was judged reliability 3 in the assessment, although this fact was not evident from the SIAP. Overall, the SIAP concluded that "*It can be predicted that all members of the category may be carcinogenic due to their in vivo genotoxic activity*." Three of the five participants did not classify based on the insufficiency of the data, but recognised that there were indications of effects from this invalid study; the other two participants classified in Cat. 2 based on this study taken together with the genotoxicity profile. Again, this may have been a result of using the SIAP in isolation (so were unaware of the study's reliability score), or the participants may have felt that, upon review, the study was in fact reliable and useable for classification purposes.

22. For **single exposure specific target organ toxicity** (STOT SE), four of the five participants did not classify based on data insufficiency or because they felt there were no relevant data. The only available study that employed a single test dose for 2,4-dimethylaniline is the acute toxicity (oral) study, but this only investigated mortality and not sub-lethal effects or clinical parameters. The underlying study for the remaining participant's classification (Cat. 1 based on blood effects at 250 mg/kg bw) is unclear, but may have been data not considered in the SIDS assessment.

23. For **repeat exposure specific target organ toxicity** (STOT RE), a valid (reliability 1) 28-day study in rats (oral gavage) at 2, 10 and 50 mg/kg bw/day was available, according to OECD 407 (NITE, Japan, 2002). The NOAEL was considered to be 2 mg/kg bw/day based on hematological effects and changes in the kidney and liver. All five participants cited this study in their classification proposals, however three classified into category 1 based on the NOAEL whereas one participant classified into category 2 based on decreased haemoglobin in females at 50 mg/kg. The remaining participant did not classify.

24. The GHS specifies that substances placed in STOT RE category 1 are "*presumed to have the potential to produce significant toxicity in humans*" based on human cases, epidemiological studies or animal studies in which significant and/or severe toxic effects were observed at low doses, whereas category 2 substances are "*presumed to have the potential to be harmful to human health"*, generally based on animal studies in which significant toxic effects were observed at moderate doses. In terms of doses, section 3.9.2.9 of the GHS gives ranges for category 1 classification in the rat for the oral route of 0 – 10 mg/kg bw/d, and for category 2 of 10 – 100 mg/kg bw/d. The explanatory text states that these values are based on a 90-day study, and it is stated that the ranges would need adjustment for shorter or longer duration studies on a case-by-case basis, using expert judgement. Paragraph 3.9.2.9.5 of the GHS gives the example of increasing the dose values by a factor of three for a 28-day study, i.e. giving approximate ranges of 0 – 30 mg/kg bw/d for Cat. 1 classification and 30 – 300 mg/kg bw/d for Cat. 2 classification. All four of the participants classifying (into Cat. 1 or Cat. 2) have done so according to this guidance. The difference in classification proposals seems to have arisen from the important question of what constitutes a significant or severe toxic effect, even though the agreed NOAEL represents *adverse* haematological

effects. The participant that did not classify did not do so because details on severity or adversity of the observed effects were not detailed enough; presumably, the participant classifying into category 2 (haemoglobin effects at 50 mg/kg bw/d) did so because they felt it was only at this dose that effects were of sufficient severity to indicate "…*the potential to be harmful to humans*". (Note that some of the reliable toxicokinetic information in the SIDS dossier indicates adverse effects in the liver following repeat exposure, albeit at higher doses, for example Magnusson et al 1971).

25. For **aquatic chronic toxicity**, no measured data on the substance were available. The most sensitive species in acute studies in two taxa (invertebrates and algae) was the invertebrate *Daphnia magna* (48h EC_{50} of 9.9 mg/l). Although no measured acute data in fish were available, other category members indicated that fish were the least sensitive species out of fish, invertebrates and aquatic plants. No ready biodegradability test was available for the substance, but an inherent biodegradation study (equivalent to OECD 302C) showed 0 % degradation (by BOD) (CERI, 1981). Four ready tests were available for four other category members. All were not readily biodegradable, and showed very low levels of degradation. The substance is not susceptible to hydrolysis at environmentally relevant pH. Therefore the SIDS assessment concluded that the substance is not readily biodegradable. Using the "surrogate" system for chronic classification (i.e. the combination of acute toxicity data with information on degradability), the daphnia acute toxicity data in combination with the degradability data would mean the substance would be classified into aquatic chronic category 2, in accordance with table 4.1.1 b) part iii) of the GHS (4^{th} ed). Three out of the six participants followed this approach.

26. Chronic toxicity data in invertebrates (*Daphnia magna*) and algae for the five other members of the dimethylaniline category were available, with *Daphnia magna* being identified as the more sensitive species (no chronic data for fish were available). The chronic daphnia data were as follows (table 3, taken from the SIAR).

Table 3: Available Chronic Toxicity Data for the Most Sensitive Species for the Dimethylaniline Category

Test substance (CAS No.)	Species	Method	Result (mg/L)	Reliability	Reference
2,3-Dimethylaniline (87-59-2)	*Daphnia magna*	Provisional procedure proposed by Federal Environmental Agency (Umweltbundesamt) Semi-static	21d NOEC = 0.1 reproduction	2	Kühn *et al.*, 1989b
2,4-Dimethylaniline (95-68-1)			21d NOEC = 0.0095 reproduction		Read Across
2,5-Dimethylaniline (95-78-3)	*Daphnia magna*	OECD TG 211 semi-static	21d NOEC = 0.096 reproduction	1	MOE, Japan, 2009g
2,6-Dimethylaniline (87-62-7)	*Daphnia magna*	OECD TG 211 semi-static	21d NOEC = 2.23 reproduction	1	MOE, Japan, 2003d
3,4-Dimethylaniline (95-64-7)	*Daphnia magna*	OECD TG 211 semi-static	21d NOEC = 0.0095 reproduction	1	MOE, Japan, 2005d
	Daphnia magna	Provisional procedure proposed by Federal	21d NOEC = 0.01 reproduction	2	Kühn *et al.*, 1989b

		Environmental Agency (Umweltbundesamt) Semi-static			
3,5-Dimethylaniline (108-69-0)	*Daphnia magna*	OECD TG 211 semi-static	21d NOEC = 0.03 reproduction	1	EA, Japan, 1998e

27. When chronic data are available for two trophic levels the GHS recommends that both the "surrogate" approach (as described above, following table 4.1.1 (b) part iii. and Decision Logic 4.1.3c of the GHS) as well as the "direct" approach using the more sensitive chronic data (in combination with the degradation information, i.e. following table 4.1.1 (b) part i. or ii. and Decision Logic 4.1.3b of the GHS) are used, and the more stringent result of the two approaches is used in the chronic classification.

28. The other three participants in the exercise used the chronic daphnia data read across agreed in the SIDS assessment (see table 3; the NOEC of 0.0095 mg/l for 3,4-dimethylaniline was selected as "worst case" read across to 2,4-dimethylaniline in the SIDS assessment) following this "direct" approach, in accordance with the GHS guidance. This resulted in a more stringent classification into aquatic chronic category 1 (one participant also derived an M factor of 10).

29. For the aquatic chronic endpoint, the main issue is clearly whether it can be justified to use this read across for the purposes of classification (the read across approach and assigned numeric value as agreed in the SIDS assessment is briefly discussed below).

30. There is a clear preference in the GHS to use chronic data, when available, for the chronic aquatic classification, despite this system's relatively recent introduction (rev. 3, 2009) and the fact that acute study protocols are generally more highly standardised. The GHS, however, makes no explicit reference to read across in its main text. In the human health section (paragraph 3.7.2.3.1 referring to toxicity for reproduction), it is stated "*Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scare*". However this is more likely to be relevant for the classification of mixtures and not read across between structurally related molecules, as is the issue here. In the environment section of the GHS, paragraph 4.1.2.13 describes the potential use of QSAR under certain circumstances and for particular endpoints, and this is expanded upon in Annex 9 (Guidance on hazards to the aquatic environment). Specific references to the use of read across in Annex 9 are as follows.

- In the section dealing with biodegradation, for cases where measure data are not available (and in the context that some information is better than none because the default classification, that a substance is not rapidly degradable, may be overly-conservative), it is stated "…*as well as expert judgement, for example, when degradation data for structurally analogue compounds are available, but such judgement should be conducted with great care*" (paragraph A9.4.2.4.14.2). However, section A9.4.4 (decision scheme) suggests that read across should only be used to support a conclusion of a lack of rapid degradation (i.e. "negative" read across). (The ECHA guidance – see below – which reproduces and builds on the GHS Annex 9 guidance, concurs on this point (section 4.1.3.2.3.2)).

- In the section dealing with bioconcentration, for cases where no measure data (log Kow or BCF) are available and no predicted Kow is available, "…*the potential for bioconcentration in the aquatic environment may be assessed by expert judgement. This may be based on a comparison of the structure of the molecule with the structure of other substances for which experimental bioconcentration or log Kow data or predicted Kow are available*."

31. In some OECD regions guidance for the GHS (or equivalent transposed legislation) is available that covers the use of read across in classification. In the EU for example, guidance[5] available through the European Chemicals Agency (ECHA) to the Classification, Labelling and Packaging (CLP) regulation[6] (Regulation (EC) No 1272/2008, amended Regulation (EU) No 286/2011 and No 487/2013) covers the use of read across and grouping approaches in classification in a reasonable level of detail. The CLP regulation itself makes reference as follows to read across in the main text (Article 6(5) and in its first Annex (section 1.1.1 "*The role and application of expert judgement and weight of evidence determination)*:

> *"Where no or inadequate test data…are available, the manufacturer, importer or downstream user shall use other available information on individual substances and similar tested mixtures which may also be considered relevant for the purposes of determining whether the mixture is hazardous, provided that that manufacturer, importer or downstream user has ascertained that information to be adequate and reliable for the purpose of the evaluation pursuant to Article 9(4)." [Art 6(5)]*
>
> *"Where the criteria cannot be applied directly to available identified information, or where only the information referred to in Article 6(5) is available, the weight of evidence determination using expert judgment shall be applied…A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across)..."* [Annex I section 1.1.1]

32. Section 1.4 of the ECHA guidance gives an overview of alternative methods for meeting the needs of classification and refers to ECHA's guidance for the REACH regulation[7] (chapter R6, QSARs and Grouping of Chemicals; R.6.2.2.1)[8] for further technical guidance. In chapter 4 (which covers the environmental classification), little if any mention of read across approaches is made, and none of the example classifications given in section 4.1.3.4 include the possibility that read across data could be used. However, in ECHA's guidance for the REACH regulation (chapter R6, QSARs and Grouping of Chemicals; R.6.2.2.1 a), it is clearly indicated that read across data can be used for classification purposes

("Under REACH, the result of read-across should be adequate for classification and labelling, risk assessment or PBT (vPvB) assessment, which implies the need for both qualitative and quantitative read-across, depending on the particular situation").

33. In addition, ECHA's REACH guidance (chapter R.6.2.2.1, *c) Quantitative Read Across*) suggests four general options for the application of quantitative read across, as follows:

- "by using the endpoint value of a source chemical, e.g. the closest analogue in a (sub)category
- by using an internal QSAR to scale the available experimental results from two or more source chemicals to the target chemical
- by processing the endpoint values from two or more source chemicals (e.g. by averaging, by taking the most representative value)
- by taking the most conservative value of the closest analogues or the most conservative value in the (sub)category

[5] available at http://echa.europa.eu/documents/10162/13562/clp_en.pdf

[6] Available at http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/index_en.htm

[7] The EU Registration, Evaluation and Authorisation of Chemicals Regulation

[8] Available at http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

34. In the case of aquatic chronic toxicity for 2,4-dimethylaniline for hazard assessment, the SIDS assessment used the last of these options for quantitative read across. The potential classification outcomes for each of the read across approaches are explored below:

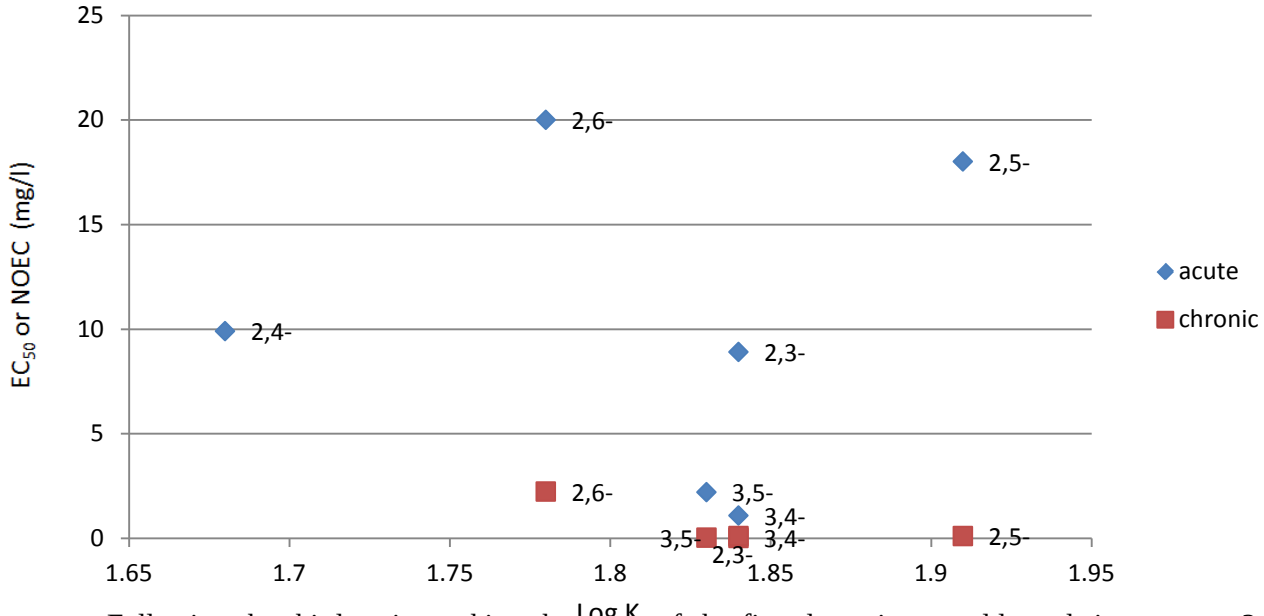
- Using the first option could result in classification into category 1 or no classification. Of the five data points there is one obvious "outlier" in terms of toxicity and classification category in the group (the 2,6-analogue, NOEC 2.23 mg/l, no chronic classification); the other four analogues are chronic category 1 substances. This approach could be problematic since no system for selecting the "closest analogue" was proposed in the assessment; ascribing chronic toxicity potential on the basis of the molecules' methyl substitution pattern with no knowledge of the underlying mode or mechanism of action is not straightforward. The available results do not seem to be related to whether the test molecule has *ortho*, *meta* or *para* substitutions (to the amine group).

- The second option, producing an internal QSAR (or carrying out trend analysis), is not easy since there is no obvious co-variable against which to plot the toxicity data. Acute data is often plotted against log Kow for trend analysis, since the non-polar narcosis mode of action ("baseline" toxicity) is driven by hydrophobicity. In the absence of any other clear variable in this case, the chronic data could be plotted against measured log Kow. Table 4 below lists log Kow, acute and chronic data along with the classifications that would be reached based on the measured acute and chronic daphnia data (assuming that all substances are not rapidly degradable, as was concluded in the SIDS assessment). However all the substances have very similar log Kow values, and no trend is apparent in the resulting scatter plot from these data (figure 1). Note again that in all cases where measured data exist (acute and chronic), daphnia was the most sensitive species. It is interesting to note that sequentially the acute and chronic toxicity follow much the same order, although the acute:chronic ratio is rather variable.

Table 4: Available Acute and Chronic *Daphnia Magna* Toxicity Data for the Dimethaniline Category

Substance	**Log Kow**	**Acute Daphnia EC_{50} (mg/l)**	**Chronic Daphnia NOEC (mg/l)**
3,4-dimethylaniline	1.84	1.09 → Chronic Category 2	0.0095 → Chronic Category 1
3,5-dimethylaniline	1.83	2.2 → Chronic Category 2	0.03 → Chronic Category 1
2,3-dimethylaniline	1.84	8.9 → Chronic Category 2	0.1 → Chronic Category 1
2,4-dimethylaniline	1.68	9.9 → Chronic Category 2	No data -
2,5-dimethylaniline	1.91	18 → Chronic Category 3	0.096 → Chronic Category 1
2,6-dimethylaniline	1.78	20 → Chronic Category 3	2.23 → Not classified

Figure 1: Plot of Acute and Chronic *Daphnia Magna* Toxicity Data for the Dimethaniline Category against log Kow



- Following the third option, taking the mean of the five datapoints would result in category 2 classification, but is heavily influence by the least sensitive result (the 2,6-analogue data; excluding this data point would result in category 1 classification).

- Because of the uncertainties with the other read across approaches briefly explored above (inability to distinguish structural closeness with respect to chronic toxicity, lack of a suitable co-variable related to toxic mode of action, and the fact that four out of the five substances for which measured chronic data are available would be classified into category 1), the read across approach for quantitative data taken in the SIDS assessment could be considered the most defensible.

Second Phase: CoCAM 5 revisit

35. Given the results at CoCAM 4 – a significant level of divergence – it was decided to continue the exercise to CoCAM 5 for selected endpoints for 2,4-dimethylaniline (see paragraph 10).

36. The results submitted by the six countries for the four endpoints with rationales, along with an indication of the level of detail required for the proposal (i.e. whether classification was possible using the SIAP alone, or whether the SIAR, or SIAR and then dossier needed to be consulted) are shown below in table 5. The classifications that were proposed in the first phase by the Netherlands, Switzerland and the Russian Federation, taken from Table 2, are included for comparative purposes. As was done for Table 2 above, the table is split into two parts: the first with endpoints for which consensus was reached and the second for endpoints for which this was not the case.

Table 5: Classification Proposals for Selected Endpoints for 2,4-Dimethylaniline (CAS 95-68-1) in Phase Two of the Exercise (Phase One Proposals Included for Comparison)

Part 1: Selected Endpoints for which Classification Proposals were the same						
	Country					
Endpoint	**NL**	**DK**	**CH (HH only)**	**RO**	**FR**	**JP (HH only)**
2,4-dimethylaniline: Carcinogenicity	**Cat 1B or 2**	**possible Cat 2**	**Cat 2**	**Cat 2**	**Cat 2**	**Cat 2**
rationale	**read across/WoE**: 2,6- analogue rat study; supporting studies for 2,4- itself & 2,5- analogue	**read across/WoE**: 2,6-analogue rat study; supporting studies for 2,4- itself & 2,5- analogue	pulmonary tumours (mice); *in vivo* genotoxicity	pulmonary tumours (mice); *in vivo* genotoxicity	pulmonary tumours (mice); *in vivo* genotoxicity	**read across/WoE**: 2,6-analogue rat study; supporting studies for 2,4- itself & 2,5- analogue
level of detail	IUCLID	SIAR	SIAP	SIAR	SIAR	IUCLID
CoCAM 4 proposal	not classified data not sufficient		Cat. 2 same basis	Cat. 2 same basis		
Part 2: Selected Endpoints for which Classification Proposals differed						
Endpoint	**Country**					
	NL	**DK**	**CH (HH only)**	**RO**	**FR**	**JP (HH only)**
2,4-dimethylaniline: Acute Toxicity (oral)	**Cat 4 (3)**[1]	**Cat 4**	**Cat 3**	not classified (**cat 3**)[1]	**Cat 4 (3)**[1]	**Cat 3**
rationale	**read across**: 2,6-analogue LD_{50} 300 - 2000 mg/kg bw (female mice)	**read across**: 2,6-analogue LD_{50} 300 -	LD_{50} 250 mg/kg bw (mice)	data not sufficient (rel 4 study)	read across/WoE approach: 2,6-	LD_{50} 250 mg/kg bw (mice)

		2000 mg/kg bw (female mice)			analogue LD_{50} 300 - 2000 mg/kg bw (female mice)	
level of detail	IUCLID		SIAP	IUCLID	IUCLID	SIAP
CoCAM 4	Cat. 3 (o)		Cat. 3 (o)	not classified		
proposal	Mouse LD_{50} 250 mg/kg		same basis	data not sufficient		
STOT RE oral	**Cat 1 or 2**	**Cat 1 or Cat 2**	not classified	**Cat 1**	not classified	**Cat 1**
rationale	NOAEL 2mg/kg bw/day; blood, liver & kidney effects at 10 mg/kg bw/day	NOAEL 2mg/kg bw/day; blood, liver & kidney effects at 10 mg/kg bw/day	data not sufficient	NOAEL 2mg/kg bw/day; blood, liver & kidney effects at 10 mg/kg bw/day	data not sufficient (details lacking on observed effects)	NOAEL 2mg/kg bw/day; blood, liver and kidney effects at 10 mg/kg bw/day
level of detail	IUCLID	SIAP	IUCLID	IUCLID	SIAR	SIAR
CoCAM 4	cat 1		not classified	cat 1		
proposal	same basis		same basis	same basis		
2,4-dimethylaniline: Chronic Aquatic toxicity	Cat 1	Cat 1	not reported	Cat 2 (Cat. 1)[2]	Cat 1 (M 10)	not reported
rationale	read across: no rapid deg & NOEC (3,4-analogue)	read across: no rapid deg & NOEC (3,4-analogue)		surrogate approach on "own" data (read across: no rapid deg (NOEC, 3,4-analogue)[2]	read across: no rapid deg & NOEC (3,4-analogue)	
level of detail	IUCLID	SIAP		SIAR	SIAP	
CoCAM 4	Cat. 1 (cat 2 "own"		Cat. 2	Cat. 2		Cat. 1

	data)					
rationale	same basis		surrogate approach on "own" data	same basis		read across: no rapid deg & NOEC 0.0095 mg/L (3,4-analogue)

[1] the OECD 407 study was upgraded from reliability 4 to 2; during discussions at CoCAM 5 participants agreed that had the final study summary been available with this reliability, they would have used it to classify into category 3.

[2] during discussions at CoCAM 5 and by subsequent written comment, RO indicated that the substance's own data should probably be used in preference to read across data, but that if read across resulted in a more stringent classification and could be justified it would be considered.

37. For **acute toxicity (oral route)**, one country consulted all three SIDS assessment documents and decided that the available information was insufficient for classification purposes (the OECD 407 study in mice and rats with reliability 4). Two countries used the study to classify into category 3, consulting the SIAP in isolation. This highlights the same issue as described in paragraph 16; how supporting data are reported in the SIAP. Based on read across from the 2,6-analogue having consulted all three SIDS documents, the remaining three participants classified into category 4. Unfortunately the revised SIDS dossier was not available for this exercise, in which the OECD 407 study had been upgraded from reliability 4 to 2. This was explained to the participants at CoCAM 5, and they all agreed that the study was likely therefore to be useable and so they would probably have classified into category 3.

38. For **repeat exposure specific target organ toxicity** (STOT RE), a reliable study in the rat was available but the SIDS documents, including the dossier's robust study summary, do not clearly describe the severity of the observed effects, as described in paragraph 24. For this reason, two countries felt the data were insufficient for classification. The other four countries proposed classification into category 1 (or 2) based on effects in the blood, liver and kidney observed at 10 mg/kg bw/day (and the NOAEL of 2 mg/kg bw/day) in this study. Again, differences are apparent because of lack of detail in the study description with respect to adversity and severity of the effects (although they are used to derive a NOAEL rather than a NOEL).

39. The **carcinogenicity** endpoint has been included in part 1 of table 5, although equally it could be argued it should appear in part 2. Although the same classification was (almost) reached, the basis for the classification for half the proposals differed: three of the countries used the available study in mice for the substance to propose category 2, whereas the other three countries felt this study was insufficient and used a read-across/weight of evidence (WoE) approach to arrive at the category 2 proposal (the same mice study was included as part of this WoE argument).

40. For the chronic aquatic toxicity endpoint, the same issues as in the first phase of the exercise were apparent around the use of read across. This highlights the need to elaborate a watertight argument to justify a specific quantitative read across approach.

Nonane (CAS 111-84-2)

41. Table 6 displays the classifications that are available in OECD member countries for nonane for endpoints commonly reported in a SIDS assessment. These are given for information only; unfortunately the basis and rationale for these classifications is not reported, so any differences that are apparent cannot be explored here.

Table 6: Classifications available for Nonane in the EU, Japan and New Zealand

Endpoint	ECHA-CHEM[1]	GHS-J	HSNO CCID[2]
Skin sensitisation	not classified (15/15)	not classified	not classified
Mutagenicity	not classified (15/15)	not classified	not classified
Carcinogenicity	not classified (15/15)	not classified	not classified
STOT RE	not classified (15/15)	not classified	not classified
Reproductive Toxicity	not classified (15/15)	not classified	not classified
Aspiration toxicity	Cat 1 (13/15)	Cat 1	not classified

Acute Toxicity	Cat 4 (i) (7/15) Not classified (7/15)	Cat 4 (i)	6.1D (i) (Cat. 4) 6.1E (o) (Cat 5)
Skin irritation	Cat 2 (8/15) Not classified (7/15)	Cat 2	6.3B (Cat 3)
Eye Irritation	Cat 2 (8/15) Not classified (7/15)	Cat. 2A 2B[3]	6.4A (cat 2A/B)[3]
STOT SE	Cat 3 (11/15)[4]	Cat 3[4]	not classified
Aquatic Acute Classification	not used	Cat 1	9.1A (Cat. 1)
Aquatic Chronic Classification	Not classified (7/15) Cat. 1 (4/15) Cat 4 (3/15)	Cat. 2	9.1A (Cat. 1)

Notes:
Endpoints ordered as per Table 7 for ease of comparison.
[1] the ECHA classification database had 15 entries for the substance for 396 notifiers at the time of searching for this exercise (end November 2012). The classifications reported in the table refer to those most commonly reported for each endpoint by entry, with the number in brackets showing the number of entries with this classification out of the total of 15; for endpoints with significant numbers of other notified classifications these are also given.
[2] Classifications in New Zealand are categorised according to HSNO Hazard Classes; the GHS equivalent is included in brackets (according to http://www.epa.govt.nz/publications/hsnogen-ghs-nz-hazard.pdf)
[3] GHS-J and HSNO do not use sub-categories for reversible eye effects.
[4] Some classifications in the EU notifications based on read across; GHS-J based on read across.

First Phase: CoCAM 4

42. A summary of the classifications received for nonane in the exercise's first phase from the Netherlands, Switzerland, Italy, Russia, Japan (environment only) and BIAC (JCIA) is given below in table 7. Again, endpoints for which there was consensus are listed in "part 1" and endpoints for which classification proposals diverged are given in "part 2". Under each classification proposal (or lack of a proposal) a summary of its basis is given. Some patterns are evident in the differences, and as was the case for 2,4-dimethylaniline these will be explored below endpoint-by-endpoint.

43. As described in paragraph 5, nonane was assessed as part of the category C9-C14 Aliphatic Hydrocarbon Solvents, which included linear chain, iso-paraffins and some complex hydrocarbons. This means that for some studies relevant for nonane the tested material may have actually been a complex mixture of hydrocarbons. Differing levels of straight chain C_9 (ie nonane) may have been present in test materials in such tests. Hence the delineation between what constitutes substance test data and what constitutes read across is not straightforward in this case. The SIDS assessment describes in as much detail as was available the tested substances' composition for each endpoint, and the participants in this exercise took this information into account in their submissions.

44. For nonane there was a slightly greater number of endpoints for which participants agreed in their proposals for classification than there were for 2,4-dimethylaniline (6/12 as opposed to 5/12), but this may be misleading since these were almost all proposals for no classification. Although only those endpoints in part 2 of table 7 are discussed below (diverging proposals), a few points about part 1 of table 7 should be noted (endpoints for which proposals were the same). All participants proposed the same classification for

skin sensitisation, although the Netherland's basis for this differed from the other participants as the Netherlands restricted their basis for proposals to the SIAP in this part of the exercise. For chronic aquatic toxicity, only one chronic study was available for nonane (a NOEC of 0.005mg/l in *Daphnia magna*) so proposals were derived following the GHS using the more stringent result from the surrogate and direct approaches, as was the case with 2,4-dimethylaniline. However, proposals appeared to have been omitted accidentally or incorrectly reported by two participants; these differences are not considered in this analysis so this endpoint appears in part 1 of table 7. Further, for those participants classifying into category 1 there were some differences in the interpretation of the substance's potential for degradation (although this did not affect the classification because of the substance's high log Kow, and the fact that the NOEC was within the GHS category 1 criteria for both rapidly and non-rapidly degraded substances).

45. For **aspiration toxicity**, four out of five participants classified into category 1 based on physico-chemical properties (low viscosity). The Netherlands did not classify and did not expand on the reason for this, although it is likely that the lack of a proposal was because viscosity was not reported in the SIAP (the participant used the SIAP in isolation for proposals in this part of the exercise).

46. For **Acute toxicity (inhalation)**, three participants proposed no classification. They used an 8h LC_{50} from an OECD 403 study in the rat (Nilsen et al, 1988)), cited in the SIAP:

> "Acute inhalation studies conducted according to, or similar to OECD TG 403…demonstrated that the LC50 value for nonane was 23775 mg/m^3…"

The remaining participant classified into category 4 for the inhalation route based on an LC_{50} of 3200 ppm in the rat from a non-SIDS data source (American Conference of Governmental Industrial Hygienists).

47. For **Acute toxicity (oral)**, no data on the substance were available. Proposals for no classification were made by the five participants; three of the five used read across for this conclusion (higher molecular weight category members with LD_{50} values from 5 to 15.8 g/kg). One participant did not classify based on no data, and no information was submitted by the remaining participant.

48. For **Acute toxicity (dermal)**, no data were available for the substance. Proposals for no classification were made by four of the five participants, with three basing this on read across and one basing it on no data (as for the oral route); one participant classified into category 5 based on category member read across (because the read across did not guarantee the LD_{50} value would be >5000 mg/kg).

49. For **skin corrosion/irritation**, two participants used non-SIDS data or conclusions to classify into category 2 whereas the other three participants proposed no classification based on insufficient data (the assessment concluded that category members produce minimal to slight irritation in rabbits and that defatting of the skin in humans can cause irritant dermatitis, but lacked details on scoring, observation time, etc).

50. Similarly for **eye damage/irritation**, a participant used a non-SIDS conclusion to classify as category 2, whereas the other four participants proposed no classification owing to insufficient data (the assessment concluded that category members produce minimal to slight irritation in rabbits but again lacked details on scoring, observation time, etc).

51. For **single exposure specific target organ toxicity** (STOT SE), three of the five participants classified into category 3 based on read across (effects on the central nervous system in other category members with similar chain lengths). Some of the participants took a weight of evidence approach, based on the read across data, key nonane acute inhalation toxicity study (which also reported acute CNS effects) and effects in humans (although some non-SIDS information was also cited). The remaining two

participants did not propose any classification and did not follow a read across/weight of evidence approach.

52. Classification proposals for **acute aquatic toxicity** were as follows: five of the six were for category 1 classification, whereas one proposal was for no classification based on insufficient data. However, the classification proposals could have shown a greater variety because of the way information was reported in the assessment (use of ranges for effect results, as recommended in the OECD manual for the cooperative assessment of chemicals):

> *"Paraffinic hydrocarbons with a carbon number of 10 and below, are expected to exhibit acute aquatic toxicity in the range of 1 to 10 mg/L (based on nominal loadings), although measured LC_{50} and EC_{50} values of 0.01 to 0.2 mg/L have been reported."*

The measured value for the substance is actually an EC_{50} of 0.2 mg/l in *Daphnia magna*. Although the SIAP reported range results in category 1 classification, the derived M factor could vary depending on what part of the range the proposer took to derive it (the GHS states that an M factor of 10 should be derived if the EC_{50} is in the range 0.01 – 0.1 mg/l, and an M factor of 1 for EC_{50}s 0.1 – 1 mg/l is given). In this exercise all classifying participants chose an M factor of 1, although the basis for this seems incorrect for one participant.

Table 7: Classification Proposals for Nonane (CAS 111-84-2) in the Exercise's First Phase (CoCAM 4)

Part 1: Endpoints for which Classification Proposals were the same						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP (ENV only)**
Skin sensitisation	not classified	not classified	not classified	not classified	not classified	
rationale	no data	**read across**: data sufficient	**read across**: data sufficient	**read across**: data not sufficient	data not sufficient	
Mutagenicity	not classified	not classified	not classified	not classified	not classified	
rationale	**read across**: data sufficient	data sufficient (non-SIDS)	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	
Carcinogenicity	not classified	not classified	not classified	not classified	not classified	
rationale	**read across**: data not sufficient	**read across**: data not sufficient	**read across**: data not sufficient	**read across**: data not sufficient	data not sufficient	
STOT RE	not classified	not classified	not classified	not classified	not classified	
rationale	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	
Reproductive Toxicity	not classified	not classified	not classified	not classified	not classified	
rationale	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	**read across**: data sufficient	
Aquatic Chronic toxicity	**Cat 1** (M factor = 1)	**Cat 1** (M factor = 1)	not classified[1]	**Cat 1**	not classified[2]	**Cat 1**
rationale	Daphnia NOEC = 0.005 mg/L; read across: rapidly biodegradable	Daphnia NOEC = 0.005 mg/L	no data (lacking chronic data)[1]; predicted rapid biodegradation	Daphnia NOEC = 0.005 mg/L; read across: rapidly biodegradable	rationale not given[2]	Daphnia NOEC = 0.005 mg/L, not readily biodegradable
Part 2: Endpoints for which Classification Proposals differed						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP (ENV only)**
Aspiration toxicity	not classified	**Cat 1**	**Cat 1**	**Cat 1**	**Cat 1**	
rationale	no data	phys-chem data	phys-chem data	phys-chem data	phys-chem data	
Acute Toxicity	not classified	not classified	not classified	**cat 5 (d)**	**Cat 4 (i)**	

rationale	data sufficient: OECD 403 (i); **read across** (o, d)	data sufficient: OECD 403 (i); no data (o, d)	**read across**: data sufficient	data sufficient: (i); **read across**: (o, d)	LC_{50} (rat) 3200 ppm (ACGIH)	
Skin irritation	not classified	Cat 2[3]	not classified	not classified	Cat 2[3]	
rationale	data not sufficient	non-SIDS data[3]	data not sufficient	data not sufficient	Non-SIDS data[3]	
Eye Irritation	not classified	not classified	not classified	not classified	Cat 2[3]	
rationale	data not sufficient	data not sufficient	data not sufficient	data not sufficient	Non-SIDS data[3]	
STOT SE	**Cat 3**	not classified	not classified	**Cat 3**	**Cat 3**	
rationale	**read across/WoE**: CNS effects	no data	no data	**read across**: CNS effects	**read across**: CNS effects	
Aquatic Acute toxicity	**Cat 1** (M factor = 1)	**Cat 1** (M factor = 1)	**Cat 1**	**Cat 1**	not classified	**Cat 1**
rationale	EC_{50}s 0.01 - 0.2 mg/L for ≤C10 substances (M factor based on 0.01 mg/l)	EC_{50} 0.2 mg/L (invertebrates)	EC_{50} 0.2 mg/L (invertebrates)	EC_{50} 0.2 mg/L (invertebrates)	data not sufficient	EC_{50}s 0.01 - 0.2 mg/L for ≤C10 substances

Notes:
"data sufficient" means that data relevant for the endpoint were available and could be used for classification purposes; "data not sufficient" means that data relevant for the endpoint were available, but that there was some shortcoming that meant the data could not be used for classification purposes (e.g. unreliable, or for complex endpoints lacking scoring, detail on timing, severity etc); "no data" means no data relevant for the endpoint were available; o = oral, i = inhalation, d = dermal.

[1] This appears to be a mistake as valid data for the chronic toxicity to daphnia were available for the substance. Hence this proposal is not taken into account when considering the endpoint overall.

[2] Since no rationale was given for the lack of a proposal, the proposal was omitted in consideration of the endpoint overall.

[3] non-SIDS data (reviews or conclusions of the HSDB) were used to arrive at these proposals.

Phase Two: CoCAM 5 revisit

53. The endpoint skin corrosion/irritation was selected for revisiting for nonane at CoCAM 5 to further explore use of read across and how data are presented in the assessment documents. All participants reviewed the assessment to the level of the dossier(s), and all felt that the available information was insufficient for the purposes of classification (lack of details on scoring, etc) (those participants who took part in both phases of the exercise did not change their conclusions).

54. As described above in paragraph 43, read across for this category is not straightforward. No study with nonane is available for skin corrosion/irritation; the only available studies with straight chain alkanes are with the complex substance "Hydrocarbons, C11 – 14, n-alkanes" (two semi-occlusive patch studies, resulting in mild irritation and no irritation). However, eight semi-occlusive patch studies with mixed aliphatic complex substances "Hydrocarbons, C9 – 14, n-alkanes, isoalkanes, cyclics" were available (results: one not irritating; four irritating; three mildly irritating). But the fact that only mean scores were reported meant that the data could not be used for classification, before the issue of read across suitability could even be considered.

Disodium EDTA (CAS 139-33-3)

55. Table 8 displays the classifications that are available in OECD member countries for disodium EDTA for endpoints commonly reported in a SIDS assessment. These are given for information only; unfortunately the basis and rationale for these classifications is not reported, so any differences that are apparent cannot be explored here.

Table 8: Classifications available for Disodium EDTA in the EU, Japan and New Zealand

Endpoint	ECHA-CHEM[1]	HSNO CCID[2]
Aspiration Toxicity	not classified (12/12)	
Skin irritation	cat 2 (6/12) not classified (6/12)	6.3B (cat 3)
Eye Irritation	Cat 2 (9/12) Not classified (3/12)	6.4A (cat 2A/B)
Skin sensitisation	Not classified (12/12)	
Mutagenicity	Not classified (12/12)	
Carcinogenicity	Not classified (11/12)	
STOT RE	Not classified (12/12)	
Acute Toxicity	Cat 4 (o) (9/12) Cat 4 (i) (1/12)	6.1E (o) (cat 5)
Reproductive Toxicity	Not classified	

	(12/12)	
STOT SE	Not classified (8/12) Cat 3 (4/12)	
Aquatic Acute Toxicity	Not used	
Aquatic Chronic Toxicity	Not classified (12/12)	

Notes:
Endpoints ordered as per Table 9 for ease of comparison.
The substance is not included in the GHS-J classification database of Japan.
[1] the ECHA classification database had 12 aggregated entries for the substance for over 1000 notifiers at the time of searching for this exercise (end November 2012). The classifications reported in the table refer to those most commonly reported for each endpoint by entry, with the number in brackets showing the number of entries with this classification out of the total of 12; for endpoints with significant numbers of other notified classifications these are also given.
[2] Classifications in New Zealand are categorised according to HSNO Hazard Classes; the GHS equivalent is included in brackets (according to http://www.epa.govt.nz/publications/hsnogen-ghs-nz-hazard.pdf)

Phase One: CoCAM 4

56. A summary of the classifications received in first phase of the exercise from the Netherlands, Switzerland, Italy, Russia, Japan (environment only) and BIAC (JCIA) is given below in table 9. As was done for 2,4-dimethylaniline and nonane, endpoints for which there was consensus are listed in "part 1" and endpoints for which classification proposals diverged are given in "part 2". Under each classification proposal (or proposal for no classification) a summary of its basis is given. For most of the endpoints listed in part 2 of table 9 different classifications were arrived at based on different data/rationales; however this was not the case for acute toxicity (oral and inhalation). The reasons for these differences are explored in the paragraphs below endpoint-by-endpoint.

57. For disodium EDTA there were a slightly greater number of endpoints for which participants agreed in their proposals for classification than there were for 2,4-dimethylaniline and nonane (7/12 as opposed to 5/12 and 6/12, respectively), but again this may be misleading since these were all proposals for no classification. The basis for two of these converging proposals for no classification differed for skin and eye damage/irritation, again because one participant used the SIAP in isolation whereas the others consulted the dossier (it is likely the participant would have reached the same conclusion had they also consulted the dossier).

Table 9: Classification Proposals for Disodium EDTA (CAS 139-33-3) received in the Exercise's First Phase (CoCAM 4)

Part 1: Endpoints for which Classification Proposals were the same						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP (ENV only)**
Aspiration Toxicity	not classified	not classified	not classified	not classified	not classified	
rationale	data sufficient	data sufficient	data sufficient	no data	no data	
Skin irritation	not classified	not classified	not classified	not classified	not classified	
rationale	data not sufficient	data sufficient	data sufficient	data sufficient	data sufficient	
Eye Irritation	not classified	not classified	not classified	not classified	not classified	
rationale	data not sufficient	data sufficient	data sufficient	data sufficient	data sufficient	
Skin sensitisation	not classified	not classified	not classified	not classified	not classified	
rationale	data sufficient	data sufficient	data sufficient	data sufficient	data sufficient	
Mutagenicity	not classified	not classified	not classified	not classified	not classified	
rationale	data sufficient	data sufficient	data sufficient	data sufficient	data sufficient	
Carcinogenicity	not classified	not classified	not classified	not classified	not classified	
rationale	**Read across** (3Na analogue): data sufficient	**Read across** (3Na analogue): data sufficient	**Read across** (3Na analogue): data sufficient	**Read across** (3Na analogue): data sufficient	**Read across** (3Na analogue): data sufficient	
STOT RE	not classified	not classified	not classified	not classified	not classified	
rationale	data sufficient	data sufficient	data sufficient	data sufficient	data sufficient	
Part 2: Endpoints for which Classification Proposals differed						
	Country					
Endpoint	**NL**	**IT**	**CH**	**RO**	**BIAC/JCIA**	**JP (ENV only)**
Acute Toxicity	not classified	**cat 4 (o)**	**cat 5 (o); cat 4 (i)**	**cat 4 (o)**	not classified	
rationale	data not sufficient (i, o); read across data not sufficient (d)	non-SIDS data (o); data sufficient (i); no data (d)	LD_{50} (rat) 2000 - 3980 mg/kg bw (o); LC_{50} (rat) >1103 mg/m3 (i); no data (d)	LD_{50} (rat) 2000 - 3980 mg/kg bw (o); data not sufficient (i); no data (d)	data not sufficient/no data (i, d, o)	
Reproductive Toxicity	**cat 2**	not classified	not classified	**cat 2**	not classified	
rationale	NOAEL 920 mg/kg bw/day (developmental	data sufficient	data not sufficient (but conclusive)	NOAEL 920 mg/kg bw/day (developmental	data not sufficient (but conclusive)	

	effects)			effects)		
STOT SE	not classified	**Cat 3**	not classified	not classified	not classified	
rationale	data not sufficient	1-day exposure study: 6/20 deaths at 1000 mg/m3	Data sufficient (LD_{50} (rat) 2000 - 3980 mg/kg bw (o))	data not sufficient	data not sufficient	
Aquatic Acute Toxicity	**Cat 2**	not classified	**Cat 3**	not classified	not classified	Not classified
rationale	**read across**: 4Na analogue algal data (EC_{50} 1.01 mg/l)	data sufficient (chelation not considered relevant)	**read-across**: 4Na analogue fish data (LC_{50} 41 mg/L) non-SIDS?	data sufficient (daphnia EC_{50} 140 mg/l)	No rationale given	Not sufficient (chelation not considered relevant)
Aquatic Chronic Toxicity	**cat 2**	not classified	**cat 3**	not classified	not classified	Not classified
rationale	**read across**: 4Na analogue algal data (EC_{50} 1.01 mg/l); not rapidly degradable	Not sufficient (chelation not considered relevant)	**read across**: 4Na analogue fish data (LC_{50} 41 mg/l) non-SIDS?; not rapidly degradable	data sufficient	data sufficient	Not sufficient (chelation not considered relevant)

Notes:
"data sufficient" means that data relevant for the endpoint were available that could be used for classification purposes; "data not sufficient" means that data relevant for the endpoint were available, but that there was some shortcoming that meant the data could not be used for classification purposes (e.g. unreliable, or for complex endpoints lacking scoring, detail on timing, severity etc); "no data" means no data relevant for the endpoint were available; o = oral, i = inhalation, d = dermal.

58. For **Acute toxicity (oral)**, out of five proposals there were two proposals for no classification (data not sufficient). In the case of these two proposals (which were based on the SIAP in isolation), the SIAP oral LD_{50} values for the substance and selected other category members are stated to be >2000 mg/kg bw, hence the inability to classify.

59. The SIAR and IUCLID reported a reliable oral study in rats with an LD_{50} of 2000 – 3980 mg/kg bw (Olson 1961); two participants used this study to classify into either category 4 or 5. The difference in category seems to have come about from a difference in the participants' interpretation of table 3.1.1 of the GHS (*table 3.1.1: acute toxicity hazard categories and acute toxicity estimate (ATE) values defining the respective categories*), where cut off values for the five acute categories are given for different exposure routes. In the exercise's first phase, one participant thought that the way the categories were represented (in ranges) in table 3.1.2 of the GHS was clearer and avoided any ambiguity (*table 3.1.2: conversion from experimentally obtained acute toxicity range values to acute toxicity point estimates for use in the formulas for the classification of mixtures*).

60. The remaining participant classified into category 4 based on a reliable oral study found only in the IUCLID dossier with the analogue substance tetrasodium EDTA (CAS 64-02-8) with an LD_{50} between 1780 and 2000 mg/kg bw. This substance was used as a supporting substance in the SIDS assessment for endpoints for which measured data were not available; this did not include acute toxicity since data were available for disodium EDTA.

61. For **Acute toxicity via inhalation**, four participants did not propose classification whereas one classified into category 4. The SIAP did not report an LC_{50} from the two available reliable studies (OECD 412 in the rat, 6h LC_{50} > 1.13 mg/l from the acute portion of a sub-acute limit dose study (BASF SE, 2010); 7h LC_{50} > 1.13 mg/l in the rat (Pinkerton and Schwebel, 1976a)), hence the "data not sufficient" basis for no classification for two participants of the four participants proposing no classification.

62. The other three participants used the same data (the two studies in the SIAR and dossier) differently to arrive at their proposals: two for no classification, one for category 4. The Cat. 4 proposal was based on the 6h LC_{50} value (the GHS category for Cat. 4 for dusts and mists is LC_{50}s between 1 and 5 mg/l); one participant did not classify based on specific information from the BASF study relating to low mortality numbers at 1mg/l and reversibility of effects after 14 days; the remaining participant felt that the "greater than" LD_{50} value was insufficient for classification.

63. For **Acute toxicity via the dermal** route, all five participants did proposed no classification. One participant who used the SIAP in isolation based this on data insufficiency using a read across approach (range of LD_{50} values for category members reported in the SIAP). The other participants based this on lack of data availability for the substance (or its close analogues).

64. For **Reproductive toxicity**, two participants proposed classification into category 2 based on the NOAEL for reproductive toxicity of 920 mg/kg bw/day cited in the SIAP for the substance in a 13-week 2-generation repeat dose study in the rat (Yang, 1952). The study is also cited in the SIAR, however the dossier entry identifies the study as supporting only with a low reliability; this is probably why the other participants did not classify (data not sufficient) but, taking into account the reported effect on reproduction, also why two participants felt the data to be "conclusive" although not useable for classification. This highlights the issue of clear data presentation in the SIDS assessment, which is not trivial for complicated category assessments.

65. For **Specific target organ toxicity single exposure** (STOT SE), three participants proposed no classification based on insufficient data for this endpoint. The remaining two participants classified into category 3 and did not classify, respectively, based on the same data. Category 3 classification was based

on the result of the reliable acute oral study cited above (Olson 1961), in which effects including congestion, edema, haemorrhage were reported after 5 days' exposure (but were reversible after 14 days). The remaining participant cited the study's LD_{50} and that clinical signs were only observed at higher doses to propose no classification. This highlights again the issue of clear data presentation in the SIDS assessment, which is not always easy when source data itself can be ambiguous or variable.

66. For **Aquatic Acute Toxicity**, interpretation of data is not straightforward since the substance's chelation effect can influence laboratory test results (lowering the bioavailability of essential nutrients) depending on the test media's composition (hard or soft water and cation, especially of iron, availability) and the species being tested. For example, in the case of aquatic plants the SIAP states:

> "*For aquatic plants, the low EC_{50} values are related to interference of some category members with essential metal nutrients in the test medium of the standard algae test resulting in nutrient deficiency in the laboratory test.*"

The assessment's conclusion for the environment stated:

> *"The amino carboxylic acid-based chelants category members possess properties indicating a hazard to the environment (acute toxicity to aquatic organisms between 1-100 mg/L). However, the toxicity is associated with the chelation of essential nutrients by the category members which may not be seen in nutrient rich environments."*

67. Based on this chelation effect, two participants did not classify for this endpoint, with a third participant also not classifying but in addition citing an acute daphnia study with an EC_{50} >100 mg/l (a further participant gave no rationale for their lack of classification). One participant used read across for algal data from tetrasodium EDTA (no algal data available for the substance) to classify as a worst case into category 2 (EC_{50} = 1.01 mg/l; BASF 1994). The remaining participant used read across of the most sensitive fish data (soft water) for tetrasodium EDTA (LC_{50} 41 mg/l) to classify into category 3, although these data appear not to be in the SIDS assessment (the substance itself had acute data for fish, LC_{50} = 320 mg/l in soft water).

68. For **Aquatic chronic toxicity**, a similar pattern as for the acute endpoint was seen. The same participants did not classify based on the chelation effect, with the other two "non-classifying" participants this time basing their proposals on the NOEC of 25 mg/l in daphnia. The other two participants again used the same read across from tetrasodium EDTA (the algal EC_{50} in one case and the fish LC_{50} in the other), in combination with a lack of rapid degradability, to assign category 2 as a worst case and category 3, respectively.

69. The same issue, relevance for the environment of chelation in laboratory tests, is apparent for both environmental endpoints. Those participants proposing no classification discounted the algal data (especially for tests conducted in soft water) whereas the remaining participant used read across algal data as a worst case. There appears to be merit in both approaches, and the SIDS assessment itself does not discount potential situations in the environment where toxicity to aquatic plants could occur (see excerpt from the conclusion for the environment above). This was a tricky issue and was not solved at CoCAM.

70. On a structural basis read across appears more simple here than for the nonane case, because the only difference between the substance and the analogue tetrasodium EDTA is the number of sodium ions (which the SIDS assessment describes as being toxicologically insignificant). In terms of aquatic testing, the difference in counter ions (Na^+ versus H^+) could possible affect pH, but at the concentrations tested this would be unlikely to have much of an effect on results.

71. For the second phase of the exercise at CoCAM 5, the purpose was to see if agreement across all endpoints was possible by taking a data-rich substance from a single-substance assessment (it was assumed this would make classification easier by limiting the data available and removing any complications to do with read across). The assessment of 2-vinylpyridine, agreed at CoCAM 2 (April 2012), was selected. Six participants (the Netherlands, Switzerland (Human Health only), the Russian Federation, Denmark, France and Japan (Human Health only)) produced classification proposals for the substance, as summarised in table 10. Again, the table is split into two parts with the first including endpoints for which there was consensus and the second part covering endpoints for which classification proposals diverged. Under each classification proposal (or proposal for no classification) a summary of its basis is given. Endpoints that in general had sufficient data for classification proposals were: acute toxicity (oral and dermal), skin corrosion/irritation, skin sensitisation, reproductive toxicity, STOT SE (oral), STOT RE (oral), and acute and chronic aquatic toxicity for the environment. For two endpoints, one or two countries felt this was not the case (for skin corrosion/irritation and for reproductive toxicity; see below).

Table 10: Classification Proposals for 2-vinylpyridine (CAS 100-69-6) received in the Exercise's Second Phase (CoCAM 5)

Part 1: Endpoints for which Classification Proposals were the same						
	Country					
Endpoint	**NL**	**DK**	**CH (HH only)**	**RO**	**FR**	**JP (HH only)**
Aspiration toxicity	not classified	not reported	not classified	not classified	not classified	not reported
rationale	no data		no data	no data	no data	
level of detail	IUCLID		IUCLID	IUCLID	IUCLID	
Acute Toxicity (inhalation)	not classified	not classified	not classified	not classified	not classified	not reported
rationale	data not sufficient	data not sufficient	data not sufficient	data not sufficient	data not sufficient	
level of detail	IUCLID	IUCLID	IUCLID	IUCLID	IUCLID	
Skin Irritation	**Cat 1B**	**Cat 1B**	**Cat 1**	**Cat 1B**	**Cat 1B**	not classified (Cat 1B indicated)
rationale	skin necrosis 48 h after 1h exposure (rabbit)	skin necrosis 48 h after 1h exposure (rabbit)	skin necrosis 48 h after 1h exposure (rabbit)	skin necrosis 48 h after 1h exposure (rabbit)	skin necrosis 48 h after 1h exposure (rabbit)	data not sufficient (detail lacking for rabbit study)
level of detail	IUCLID	SIAR	SIAR	IUCLID	IUCLID	IUCLID
Skin Sensitisation	**Cat 1**	**Cat 1**	**Cat 1**	**Cat 1B**	**Cat 1A** (or B)	**Cat 1** (subcategory not possible)
rationale	WoE: LLNA stimulation index >3;	WoE: LLNA stimulation index >3;	WoE: LLNA stimulation index >3; human patch	data sufficient (GPMT data)	WoE: GPMT 80% (lacking details),	WoE: LLNA stimulation index >3;

	human patch test ++ve	human patch test ++ve; GPMT 80%	test ++ve; GPMT 80%		human studies	human patch test ++ve
level of detail	IUCLID	SIAR	IUCLID	SIAR	IUCLID	IUCLID
respiratory Sensitisation	not classified	not reported	not classified	not classified	not reported	not reported
rationale	no data		no data	no data		
level of detail	IUCLID		IUCLID	IUCLID		
Carcinogenicity	not classified	not classified	not classified	not classified	not classified	not classified
rationale	data not sufficient	no data	no data	no tumours in mice after i.p. exposure	no data	no data
level of detail	SIAR	IUCLID	IUCLID	IUCLID	IUCLID	SIAR
Acute Aquatic toxicity	**Cat 2**	not reported[1]	not reported	**Cat 2**	**Cat 2**	not reported
rationale	fish LC_{50} 6.5 mg/l			fish LC_{50} 6.5 mg/l	fish LC_{50} 6.5 mg/l	
level of detail	IUCLID			SIAP	SIAP	
Chronic aquatic	**Cat 2**	**Cat 2** (or 1)[1]	not reported	**Cat 2**	**Cat 2**	not reported
rationale	**surrogate approach** (fish LC_{50} + not rapidly degradable); daphnia NOEC 0.9 mg/l also would give Cat 2	fish acute + biodeg; daphnia chronic data not possible to conclude cat 1 or 2*		Daphnia NOEC 0.9 mg/l	**surrogate approach** (fish LC_{50} + not rapidly degradable); daphnia NOEC 0.9 mg/l also would give Cat 2	
level of detail	IUCLID	SIAP		SIAP	SIAP	
Part 2: Endpoints for which Classification Proposals differed						
Endpoint	**Country NL**	**DK**	**CH**	**RO**	**FR**	**JP (HH only)**
Acute Toxicity (dermal)	**Cat 1**	**Cat 2 or 3**	**Cat 2**	**Cat 2**	**Cat 1**	**Cat 2**
Rationale	LD_{50} 160 mg/kg bw (guinea pig)	LD_{50} (rabbit) 640 mg/kg; LD_{50} (guinea pig) 160 mg/kg (inconclusive)	LD_{50} 160 mg/kg bw (guinea pig)	LD_{50} 160 mg/kg bw (guinea pig)	LD_{50} 160 mg/kg bw (guinea pig)	LD_{50} 160 mg/kg bw (guinea pig)
level of detail	SIAP	SIAR	SIAP	SIAP	SIAP	SIAR
Acute Toxicity	**Cat 2**	**Cat 2**	**Cat 3**	**Cat 3**	**Cat 3**	**Cat 3**

(oral)						
rationale	LD_{50} >50 <300 mg/kg bw (rat)	LD_{50} >50 <300 mg/kg bw (rat)	LD_{50} >50 <300 mg/kg bw (rat)	LD_{50} >50 <300 mg/kg bw (rat)	LD_{50} >50 <300 mg/kg bw (rat)	LD_{50} >50 <300 mg/kg bw (rat)
level of detail	SIAP	SIAR	SIAP	SIAR	SIAR	SIAR
Eye Irritation	**Cat 1**	not classified (Cat 1B indicated from skin data)	**Cat 1**	**Cat 1**	not classified	not classified (cat 1 or 2 indicated)
rationale	based on skin data	data not sufficient (detail lacking for rabbit eye study)	Based on skin data	based on skin data (eye data in rabbits not sufficient)	data not sufficient (no scoring)	data not sufficient (detail lacking for rabbit skin study & eye study)
level of detail	IUCLID	SIAR	IUCLID	SIAR	IUCLID	IUCLID
Mutagenicity	not classified	not classified	not classified	not classified	not classified	**Cat 2**
rationale	no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473)	no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473)	no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473)	no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473)	data not sufficient (no in vivo data; equivocal in vitro results)	data sufficient (+ve *in vitro* OECD TG 471, 472 & 473)
level of detail	IUCLID	IUCLID	IUCLID	SIAR	IUCLID	SIAP
Reproductive Toxicity	**Cat 2**	**Cat 2 (?)**	not classified	**Cat 2**	**Cat 2**	not classified
rationale	data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia), but possible secondary effect	data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia), but possible secondary effect	data not sufficient (unclear if OECD 421 effects are developmental or due to parental toxicity at 20 mg/kg bw/day)	data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia)	data sufficient (pup death at 50 mg/kg bw/day)	data not sufficient (effects in pups considered secondary)
level of detail	IUCLID	SIAR	IUCLID	SIAR	IUCLID	SIAR
STOT SE	not classified (i, d, o)	not classified (i, d, o)	not classified (i, d, o)	not classified (i, d, o)	not classified (i, d, o)	**Cat 3 (i)**
rationale	no data (i); data not sufficient (d); data sufficient (o)	no data (i, d, o)	no data (i); data not sufficient (d); data sufficient (o)	no data (i, d, o)	WoE: not required based on acute studies	WoE: acute, repeat dose & irritation studies indicate respiratory irritation
level of detail	IUCLID	IUCLID	IUCLID	IUCLID	IUCLID	SIAR
STOT RE (oral)	not classified	not classified	not classified	not classified	not classified	**Cat 2**

rationale	data sufficient (repeat dose effects related to local irritation)	data sufficient (repeat dose effects related to local irritation)	data sufficient (clinical signs reversible or not substance related)	data not sufficient for classification	data sufficient (repeat dose effects related to local irritation)	data sufficient (92d rat LOAEL 20mg/kg bw/day)
level of detail	IUCLID	SIAP	IUCLID	SIAR	IUCLID	SIAR

Notes: "data sufficient" means that data relevant for the endpoint were available that could be used for classification purposes; "data not sufficient" means that data relevant for the endpoint were available, but that there was some shortcoming that meant the data could not be used for classification purposes (e.g. unreliable, or for complex endpoints lacking scoring, detail on timing, severity etc); "no data" means no data relevant for the endpoint were available; o = oral, i = inhalation, d = dermal.

[1] the participant did not suggest classification as they followed the EU CLP regulation, which has only implemented an aquatic acute classification of category 1.

72. As for the cases described previously, much of the agreement in part 1 of the table 10 may be misleading since it reflects proposals for no classification based either on no data or insufficient data.

73. Skin corrosion/irritation is included in part 1 of table 10 because five of the six participants suggested category 1 classification based on severe effects in the rabbit, despite sub-categorisation differing in some cases. The remaining participant felt the data were somewhat lacking, but did state that category 1B was indicated from the rabbit data, so the difference is not considered significant enough to include the endpoint in the second part of the table.

74. Skin sensitisation has been included in part 1 of the table because all participants classified into category 1 (differences in or lack of sub-categorisation are not deemed significant enough in this exercise for inclusion in the second part of the table). For this endpoint it is interesting to note that five of the six participants used a weight of evidence (WoE) approach for the classification, although the exact studies cited did differ in some cases.

75. Carcinogenicity is also included in part 1 of the table. All participants proposed no classification for carcinogenicity, although one based this on a study in mice whereas all other participants felt no appropriate data existed, or (in one case) that the mice data were not useable (possibly because the study involved i.p. introduction of the substance).

76. Two points should be noted with regard to the aquatic classifications in part 1 of table 10. One (EU) participant did not classify for aquatic acute toxicity probably because only the acute category 1 is used in the EU. The same participant also noted that the basis for the result of the available chronic study in daphnia may change as a result of a revision to the OECD Test Guideline for this study; although the NOEC was quoted as 0.9 mg/l in the SIDS assessment, changes in the way the endpoint is calculated mean that it could be derived as <0.22 mg/l, which could create uncertainty about whether a classification into category 2 was stringent enough. The surrogate approach (fish, the most sensitive species in acute tests, LC_{50} coupled with the substance's non-rapid degradability) was the basis for three of the four proposals; the fourth used the daphnia NOEC of 0.9 mg/l to give the same result. Again, these differences were thought not significant enough to include the endpoint in part two of the table.

77. For **Acute toxicity** (**dermal**), five of the six proposals used the same guinea pig data (LD_{50} 160 mg/kg) but arrived at classifications into category 1 or 2. The difference seems to have come about for the same reason as it did for disodium EDTA for the oral route (see paragraph 59): a difference in the participants' interpretation of table 3.1.1 of the GHS. The remaining participant felt that there were shortcomings with the guinea pig study, but that the effect of these shortcomings may have only been slight and so proposed category 2 based on the guinea pig study but also included a category 3 proposal based on a rabbit study (LD_{50} 640 mg/kg).

78. For **Acute toxicity** (**oral**), differences in proposals came down to each participants' interpretation of the data with respect to the GHS (again table 3.1.1). A study with an LD_{50} range of >50 & <300 mg/kg bw in the rat was available. Two participants took the lower limit of this range to classify into category 2, whereas the other four interpreted the range to mean that category 3 was correct (the study's LD_{50} range neatly encompasses the GHS cut offs for category 2 classification (50 mg/kg bw) and category 3 classification (300 mg/kg)).

79. For **eye damage/irritation**, three different approaches were used based on skin or eye data from the rabbit. Three participants classified into category 1 based on the skin corrosion/irritation data. Two participants proposed no classification based on insufficient data, but did recognise that category 1(B) would apply if the skin data were used. The other participant used only the rabbit eye damage/irritation data and did not classify based on a lack of study detail.

80. For **Mutagenicity**, four participants proposed no classification since no *in vivo* data were available, however they recognised the *in vitro* data (three assays) as indicating a positive effect for the endpoint. Another participant proposed no classification for the same reason, but felt that the *in vitro* data were inconclusive. One participant classified into category 2 on the basis of the *in vitro* data. The point here relating to weight of evidence (although in this case for *in vitro* assays) is similar to that discussed for the 2,4-dimethylaniline case (see paragraph 19). However, the bigger issue in this case is that there are no *in vivo* data. The GHS (chapter 3.5, figure 3.5.1) states that substances in category 2:

> *"…**cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans***
> *Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:*
> *(a)...*
> *(b)…*
> *NOTE: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show structure activity relationship to known germ cell mutagens, should be considered for classification as category 2 mutagens."*

81. Below this figure in the GHS, three examples of *in vitro* mutagenicity tests are given (two of these are OECD 471 and 473). For 2-vinylpyridine, the OECD 471 (Ames test) gave mutagenic responses in *E. coli* with metabolic activation, although no mutagenicity with or without activation was observed in *S. typhimurium* in this study (other studies with *S. typhimurium*, mutagenicity was observed with activation). The OECD 473 (chromosomal aberration test) study gave positive results with and without activation. Both participants did not identify suitable analogues with positive *in vivo* test data to corroborate their proposals in their submissions (it would be interesting to see if such analogues exist, but this is beyond the scope of this exercise).

82. For **reproductive toxicity**, all participants cited the same study, but in some cases interpreted it differently. This was an OECD 421 (reproduction/developmental toxicity screening test). The SIDS assessment stated that dystocia was apparent, and the SIAP stated that "*the pup deaths observed between day 0 and day 4 of lactation in the 2 top doses suggest a developmental effect...On the basis of the dystocia at 50 mg/kg bw/day, the NOAEL for reproductive toxicity was estimated to be 20 mg/kg bw/day*." Nevertheless, some participants felt there was still some uncertainty whether the observed effects were in fact secondary (a result of parental toxicity). Two participants classified into category 2, but recognised this uncertainty might mean that this was actually not appropriate. Two participants proposed no classification based on this uncertainty. The remaining two participants felt the data to be less equivocal, and classified as category 2. This endpoint highlights that, when carrying out classification, how conclusions are worded in the SIAR/SIAP is very important with respect to how experts can arrive at differing conclusions (i.e. "*…in the 2 top doses **suggest** a developmental effect…").* Ambiguity, or scope for differences in interpretation, should be avoided as far as the data allow.

83. For the **specific organ toxicity repeated exposure** (STOT RE), three participants proposed no classification based on observed effects in the stomach relating to local site of irritation effects. One participant came to the same conclusion based on effects being reversible or not substance related, while another participant proposed no classification because data were not sufficient. The remaining participant classified category 2 using a 92-day LOAEL in the rat (stomach effects), having also considered the 28-day NOAEL in the rat of 12.5 mg/kg bw/day (stomach effects). This endpoint highlights differences in interpretation (relevance of effect) as well as to a lesser extent data selection (NOAEL from a 28-day study vs. LOAEL from a 92-day study).

Participants' comments and discussion points on the exercise

84. In the first phase of the exercise at CoCAM 4, the Netherlands submitted a list of general discussion points (see Annex 2) for discussion at the meeting, summarised as follows.

i. **Priority of data** (for the environment, if no aquatic chronic data are available for a substance but chronic aquatic data are available to do read-across, can read-across be applied or must the surrogate system based on substance-specific information be used to classify for aquatic chronic hazard?)

ii. **Read-across justification** (in a SIAP, read-across is often used to conclude on endpoints but justification for the read-across for the hazard and in the read-across section can be limited - what justification is necessary for read-across to be sufficient for C&L?)

iii. **Differentiating read-across & substance specific data** (is it necessary to differentiate between classification based on read-across and classification based on substance-specific data?)

iv. **Lack of study detail** (for corrosion/irritation endpoints classification not possible due to lack of details on scoring, observation times, number of animals etc.)

v. **SIAP level of detail** (not possible to classify complex endpoints such as carcinogenicity based only on the SIAP; no information on study quality or rationale for selecting a study over another in the SIAP)

vi. **Data in ranges** (how to interpretation and use data in ranges for classification?)

The Russian Federation agreed with these points, emphasising those relating to priority of data (i), differentiating between read across and specific data as the basis for classification (iii; they believe the difference needs to be recognised, e.g. "Aq Ch 1 (read across)) and the use of data in ranges (vi; they used the lower end of a range as the most conservative approach). Switzerland concurred with point v) above and suggested tabularising the data at the end of the SIAP for ease of reference, since in this phase of the exercise the SIAP had generally been used in isolation.

85. In the second phase of the exercise all SIDS assessment documents were used, so the issue with the SIAP (point v above) was no longer as relevant. Switzerland commented that they had the most difficulties classifying reproductive toxicity for 2-vinylpyridine, in this case because it was unclear if the effects observed were parental or true reproductive effects (see paragraph 82). Switzerland also said that proposing classifications from a single-chemical assessment was more straightforward than from a category assessment, as might be expected.

86. At CoCAM 5, the Netherlands (environment only) and the Russian Federation gave presentations on their experiences with the classification exercise at CoCAM 5. The points made in these presentations are captured above under the relevant endpoints.

87. At CoCAM 4 there was a discussion on whether the way data are reported in the SIDS assessment documents needs to change for the more complex endpoints (for example, in which documents scoring details are reported for endpoints like skin corrosion/irritation). The majority felt that so long as the data were available and their validity had been appraised, it did not matter which of the SIDS assessment documents they were in so long as they were present and clearly described, insofar as the original study report would allow.

88. Participants also estimated how long it took them to carry out their classification proposals in the case of 2-vinylpyridine. Estimates varied from half-a-day to 4 days, but the average seemed to be around about a day and a half.

Conclusions

89. Many of the conclusions from the exercise could have been predicted before the exercise was conducted, but some conclusions that were drawn were less obvious. The exercise showed that, even using the same dataset and following the same process (as was done for the second phase), it is not straightforward to arrive at the same classifications.

90. Proposals were more likely to diverge for endpoints that require more data interpretation like specific target organ effects (STOT SE & RE) and toxicity for reproduction. Endpoints that require scoring (irritation and sensitisation) appeared often to suffer from a lack of detail in study reports/robust study summaries on scoring, timing and severity. That said, for all four substances covered in this report there were divergences for acute toxicity, based around issues with study data reporting (results in ranges) and reliability.

91. Differences in classification proposals in this exercise came about for many specific reasons, although differences could be grouped as follows. In Table 11, below, an attempt has been made to summarise reasons for differences for each endpoint according to this grouping.

- **Selection of data**; examples include;
  - species selection for acute toxicity (oral), 2,4-dimethylaniline (paragraph 16)
  - use of skin corrosion/irritation data for eye damage/irritation, 2-vinylpyridine (paragraph 79)
  - use of *in vitro* data for mutagenicity, 2-vinylpyridine (paragraph 80 – 81)
  - selection of key data for STOT RE, 2-vinylpyridine (paragraph 83)
- Interpretation of data; examples include;
  - Effects basis and severity for STOT RE, 2,4-dimethylaniline (paragraphs 23 – 24 & 38)
  - Data sufficiency for carcinogenicity, 2,4-dimethylaniline (paragraph 39)
  - Use of results in ranges for acute (oral) toxicity, Na_2 EDTA (paragraphs 58 – 59) and for 2-vinylpyridine (paragraph 77)
  - Use of "greater than" results for acute (inhalation) toxicity, Na_2 EDTA (paragraphs 61 – 62)
  - Relevance of effect:
    - acute and chronic aquatic toxicity, Na_2 EDTA (paragraphs 66 – 69)
    - reproductive toxicity, 2-vinylpyridine (paragraph 82)
- Data reporting in the SIDS assessment; examples include:
  - Use of data ranges for multiple results/chemicals for aquatic acute toxicity, nonane (paragraph 52)
  - Identification of key vs. supporting studies (and reliabilities) for reproductive toxicity, Na_2 EDTA (paragraph 64)

(note that in the second phase of the exercise all SIDS documents were used, which was meant to prevent this issue since reliabilities are always reported in the dossier)

- **Use of read across/weight of evidence**[9]; examples include:
  - Mutagenicity data, 2,4-dimethylaniline (paragraphs 19 & 20)
  - Invertebrate data for chronic aquatic toxicity, 2,4-dimethylaniline (paragraphs 25 – 29 & 40)
  - Dermal data for acute toxicity, nonane (paragraph 48)
  - CNS effects for STOT SE, nonane (paragraph 51)

Table 11: Summary of reasons for differences in proposals

	Chemical			
Endpoint	**2,4-dimethylaniline**	**Nonane**	**Na_2 EDTA**	**2-vinylpyridine**
Aspiration toxicity		[Use of non-SIDS data]		
Acute Toxicity	**Selection of data**	**Use of read across**	**Data reporting/ interpretation of data**	**Interpretation of data/ Data reporting**
Skin irritation		[Use of non-SIDS data][3]		
Eye Irritation	[Use of non-SIDS data]	[Use of non-SIDS data]		**Interpretation of Data/ Selection of data**
Mutagenicity	**use of WoE**			**Selection of Data**
Carcinogenicity	**use of WoE**[1]			
Reproductive toxicity			**Interpretation of data**	**Interpretation of Data**
STOT SE	[use of non-SIDS data]	**Use of read across/use of WoE**	**Interpretation of data**	**Interpretation of Data**
STOT RE	**Interpretation of data**			**Interpretation of Data**
Aquatic Acute toxicity		**Data reporting**	**Interpretation of data**	
Aquatic Chronic toxicity	**use of read across**[2]		**Interpretation of data**	

[1]subsequently "agreed" at CoCAM 5 as likely Cat. 2
[2] subsequently "agreed" at CoCAM 5 as Cat. 1
[3]subsequently "agreed" at CoCAM 5 as not classified based on insufficient data

92. Under the grouping "interpretation of data" fall cases where the use of conditional or ambiguous language in the SIAR/SIAP can have important consequences with respect to how experts arrive at conclusions (e.g. "*…in the 2 top doses **suggest** a developmental effect…")*, although clearly there will be cases where the data are such that such language must be used.

93. Many of these issues would be difficult to solve, as they involve expert judgement (those falling under the headings of data selection, data interpretation, use of WoE/read across). Clearer and more exacting study reporting in robust study summaries would no doubt help, although this is often limited by

[9] For cases where participants used such datagap filling approaches versus those who did not, and cases where participants used them in different ways.

the level of detail available in original study reports, especially older studies conducted before modern guidelines were available.

94. How read across can be applied in classification is another case that will often come down to expert judgement for a specific case under consideration. In this exercise, read across was used for classification for several endpoints when cases were "clear cut" (see above bullet for examples). In addition, the point made by two participants relating to whether classification based on read across should be reported in a way that makes the basis clear is important and may need consideration in the future (in case classifications could be revised as a result of the generation of new substance-specific data, for example). The GHS itself does not make explicit reference to the use of read across, instead the system is built around *adequate and reliable data* (which does not exclude data from read across). Some regional guidance (e.g. in the EU for the CLP regulation) does cover the use of read across for classification, as discussed in this report. This is a sensible approach in that inclusion of such guidance in the GHS itself would over-complicate an already complicated document, and because it is clear that the same read across should be applicable and robust for use in both hazard/risk assessment and classification.

95. Work on guidance for read across and grouping approaches is on-going at the OECD and elsewhere. Indeed, the use of data that does not involve new testing is in keeping with the ethos of the GHS and OECD. However, increasing numbers of conservative classification proposals based on read across could have the undesirable effect of promoting additional testing designed to "conclude" on the endpoint. This is another reason why read across approaches, if used in classification, need to be thoroughly robust and their applicability acceptable.

96. Closely related to read across is the use of the weight of evidence approach. Depending on the available data, a WoE approach should be considered more robust than read across on its own (when read across forms one of the lines of evidence). For several cases where multiple lines of evidence are available in this report, conclusions appear to have been arrived at more easily following a WoE approach. WoE approaches are carried out according to expert judgement. It would be helpful if guidance on the use of WoE was developed for use on hazard and risk assessment and classification, insofar as this is possible for an approach that is likely to be applied in specific cases that cannot be generalised easily.

References

NOTE: full references and Robust Study Summaries for studies referenced in this report are available in the following SIDS assessments, available in the OECD Existing Chemicals Database.

Screening Information Dataset (SIDS) Assessment for the Dimethylaniline Category, OECD, 2014 available at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=d4433fd4-6765-4244-8de9-c6fab5beb978

Screening Information Dataset (SIDS) Assessment for the C9-14 Aliphatics Hydrocarbon Category, OECD, 2014 available at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=8860f974-8457-4220-9097-f00667fc0f55

Screening Information Dataset (SIDS) Assessment for the Chelants Category, OECD, 2014 available at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=fcfbe826-b29f-456c-ab30-affafff1914d

Screening Information Dataset (SIDS) Assessment for 2-Vinylpyridine, OECD, 2014 available at: http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?key=0c8de4fc-2360-4a31-a397-8c6bc742ca72&idx=0

Annex 1: Instructions for the continuation of the exercise to CoCAM 5

Pilot Exercise on Classification for CoCAM 5

Procedural instructions for the exercise following the proposal and comments submitted by 28th June.

General Points

- The SIAP, SIAR and Dossier should be consulted for classification proposals, as necessary; if more information is needed than is available in the SIAP, the SIAR and dossier should be consulted sequentially. Bear in mind that the SIAP contains usually only Klimisch scored 1 and 2 data.

- Proposals, when made, should be according to the GHS, 4th ed. (http://www.unece.org/?id=25985)

- Proposals for each endpoint should be made following the format found below, outlining the key data used for the endpoint, the classification proposed, the rationale behind the proposal and (if possible) which SIDS document needed to be consulted for the endpoint (to give information on level of detail needed).

Points for the single chemical for classification (all available endpoints): CAS 100-69-6, 2-vinylpyridine

- Although the SIAR and dossier have not been published, pre-publication versions for the assessment are now available and these are attached with the email message; please do not use the versions submitted to SIAM 34.

- As noted in Switzerland's comments, scoring data for irritation and sensitisation appear not available in the assessment documents. This may mean that classification proposals for these endpoints are again not possible.

- The Secretariat will produce an overview of the classifications that are proposed.

Points for the "Complex Endpoints" revisit from the CoCAM 4 classification exercise

Endpoints to consider for human health are as follows:

1. Carcinogenicity for 2,4-dimethylaniline

2. STOT RE for 2,4-dimethylaniline

3. Skin corrosion/irritation for nonane

And for the environment:

1. chronic aquatic toxicity for 2,4-dimethylaniline

- Please make your proposals for classification from scratch; do not copy and paste classifications put forward for CoCAM 4.

- Revisit the data in the assessments using the approach outlined for the single chemical above for each endpoint (sequential review of SIAP, SIAR and dossier).

- As the SIAR and dossier have not been published, the versions submitted for CoCAM 3 should be used in the exercise (see Clearspace or attachments to this message).

- The secretariat will produce an overview of the classifications proposed, compared against those proposed for CoCAM 4 for the same endpoints/chemicals.

A Request

Russia have suggested that we consider acute toxicity (human health) for either 2,4-dimethylaniline or disodium EDTA, since we saw different proposals due to differences in approach at CoCAM 4. Looking again at a simple endpoint would help to check our ability to take a harmonised approach when we are all working in the same way.

For this reason the Secretariat asks that you also consider acute oral toxicity for 2,4-dimethylaniline in this exercise.

Schedule
If possible please submit your proposals to the secretariat by the **2nd September** (also the CoCAM 5 deadline for comments). This should allow other member countries to review the proposals.

Format of classification proposals

Member Country (HH/ENV):
Substance:

<Endpoint>
Classification proposal:
Key Data: <study type & result or reference if taken from SIAR/dossier>
Rationale: (including details of read across, if used)
Level of detail: SIAP/SIAR/dossier (delete as appropriate)

Annex 2: Participants Discussion Points and Comments

RIVM – NL participation in the OECD C&L Pilot Exercise for selected chemicals
Experts: Lidka Maslankiewicz, Sjöfn Gunnarsdottir, Emiel Rorije, Gitte Tiesjema, Andre Muller, Jeannette Gómez Contreras and Betty Hakkert.

It was not clear which framework and edition to use for the exercise. Therefore the NL opted to use GHS and not CLP for the exercise since it is OECD activity and thus global. We used the GHS 4th from the following link:

http://www.unece.org/trans/danger/publi/ghs/ghs_rev04/04files_e.html

Proposed classifications are reported in separate documents. We would like to propose the following issues for discussion based on our experience performing this exercise.

1) Priority of data: If no aquatic chronic data are available for a substance but chronic aquatic data are available to do read-across, can read-across be applied or must the surrogate system based on substance-specific information be used to classify for aquatic chronic hazard?
2) Read-across justification: In the SIAPs, read-across is often applied to classify but the justification for the read-across for that hazard and in the read-across section is often very limited. Discussion on what sort of justification is necessary for a read-across to be sufficient to draw a conclusion on C&L.
3) Read-across vs substance specific data: Is it necessary to differentiate between classification based on read-across and classification based on substance-specific data?
4) Regarding corrosion/irritation endpoints classification was not possible due to lack of details on scoring, observation times, number of animals etc.
5) It may not be possible to classify complex endpoints such as carcinogenicity based only on the SIAP.
6) There is no information on study quality or rationale for selecting a study over another in the SIAP.
7) Application or interpretation of classification when range of values is presented.

ISS–IT participation in the OECD C&L Pilot Exercise for selected chemicals

Experts: Paola Di Prospero Fanghella, Maria Grazia Iuliano, Maria Alessandra Nania, Ida Marcello, Renato Cabella.

To carry out the pilot exercise were consulted documents made available by the OECD (SIAP, SIAR and IUCLID data set), and when considered necessary have been consulted other sources of data, such as eChemPortal and primary sources.

The SIAR and SIAP are rather poorly described for classifying for some endpoint , as shown for the endpoint of eye irritation, in which, in the studies were lacking the scores for application the criteria of classification. One example is the 2,4-dimethylaniline (2,4 DMA).

For the evaluation of chronic aquatic toxicity data are often lacking, then a possible approach is to read-across.

The use of read-across is explained in Section A 9.6.4 of the GHS and indicated in Annex I section 1.1.1 of the CLP

That value to give the read-across is still an open question, especially if for a given substance there is no valid data in the acute aquatic toxicity. Assuming that the GHS at point A 9.6.4.13 states that the calculated values of chronic toxicity with read-across cannot replace experimental data for acute toxicity.

Which priority to give between NOEC, the read-across and an EC50 on the substance itself, especially if the read-across is classified the substance in a category more restrictive? One example is the 2.4 DMA.

For the evaluation of acute toxicity by the oral and inhalation routes the test species is the rat. As described in 3.1.2.3. in the GHS and 3.1.2.2.1 in CLP.

When experimental data for acute toxicity in several animal species are available, expert judgement needs to be used to choose the most appropriate value for classification purposes. In general, the classification is based on ATE lower if you have values of different species (as reported by the ECHA guidance to the application of the criteria for classification according to CLP pag.197 and 198 paragraph 3.1.2.3.2). Example 2.4 DMA : if one considers the oral LD50 rat (470 mg / kg bw) the substance is classified in Category 4, while considering the oral LD50 topo (250 mg / kg bw) is assigned to category 3.

In this case, the purpose of classification, more information is needed on the mechanisms and studies on the metabolism of the animals. In this way you can determine what is a good animal model for the effects on humans.

In conclusion:

1) It obvious that if you are not using a unique data base there will always be different classifications.
2) The accuracy of the data reported in the SIAR and SIAP would allow expert judgment more harmonized.
3) Read across approaches, if used in classification, need to be thoroughly robust and accepted.

Annex 3: Collated Classification Proposals for CoCAM 4 and CoCAM 5 (available separately)

This annex is available as a separate document. [ENV/JM/MONO(2014)31/ANN]