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Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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No. 3, *Guidance Document for Aquatic Effects Assessment* (1995)

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About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

The work of the OECD related to chemical safety is carried out in the **Environmental Health and Safety Programme**. As part of its work on chemical testing, the OECD has issued several Council Decisions and Recommendations (the former legally binding on Member countries), as well as numerous Guidance Documents and technical reports. The best known of these publications, the **OECD Test Guidelines**, is a collection of methods used to assess the hazards of chemicals and of chemical preparations such as pesticides and pharmaceuticals. These methods cover tests for physical and chemical properties, effects on human health and wildlife, and accumulation and degradation in the environment. The OECD Test Guidelines are recognised worldwide as the standard reference tool for chemical testing.

More information about the Environmental Health and Safety Programme and its publications (including the Test Guidelines) is available on the OECD's World Wide Web site (see page 6).

The Environmental Health and Safety Programme co-operates closely with other international organisations. This document was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organization. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

FOREWORD

The Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member countries has been prepared by a Joint German and United States Working Group as part of the work being carried out in the OECD's Programme on Harmonization of Classification and Labelling Systems.

This publication was produced within the framework of the Inter-Organisation Programme for the Sound Management of Chemicals (IOMC).

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EXECUTIVE SUMMARY

A comparison of existing eye irritation/corrosion hazard classification procedures currently in use is laid out, and issues requiring resolution are discussed. Results of evaluation of eye irritancy test data submitted within the chemicals notification prodedure of the European Union are presented, demonstrating regulatory observations concerning leasons in the rabbit eye. A case study is presented to illustrate the scoring processes, and irritation data on chemicals from several sources are used to compare the sensitivity of existing classification systems. In developing potential harmonized positions for eye irritation/corrosion testing, two objectives have been kept in mind: to define criteria for both serious damage to eyes and eye irritation that are in the range of sensitivity of existing systems and to have the option of subdividing effects in two parts for those authorities that need them.

To illustrate a potential harmonized classification of irritation, the scoring procedures currently employed by the EU are put forward. Erythema/eschar and edema of the conjunctiva, iritis and corneal opacity are graded separately; an animal´s mean score from readings over the first three days after exposure must meet a defined level to be positive. The proportion of test substances expected to be positive are investigated for the possible harmonized system discussed in January 1998. The proportion of irritants would increase in comparison to existing EU and combined Canadian pesticide systems. The Canadian workplace and EPA pesticide systems may or may not decrease. Authorities wanting to have two irritation subcategories have the option of dividing the irritant class into two subclasses.

INTRODUCTION

In September 1989 the Commission of the European Communities (CEC) hosted an international seminar in Brussels entitled ”LD50 and classification schemes - the possibilities for change”. From different presentations made to the seminar it was clear that several different classification schemes based on the acute toxicity of chemicals exist in different countries, trading blocks, and other international organi- sations. The seminar concluded that rationalisation of the different schemes of clas- sification currently in use was essential if further progress in the reduction in the numbers and/or suffering of animals used in acute toxicity tests was to be achieved.

At the end of the seminar the CEC committed itself to take an initiative to evaluate the feasibility of such a rationalisation. Subsequently the scope of the project was broadened to include skin irritation, skin corrosivity, skin sensitization, and eye irritation in addition to acute toxicity.

As a consequence of the seminar hosted by the CEC, Arthur Walker established for the DG XI of the Commission of the European Communities how many schemes for classifying chemicals as dangerous, based on toxicological properties, exist and identified which national authorities or international organisations are responsible for the schemes (1). The countries/organisations covered by his work are:

- European Community (Belgium, Denmark, Federal Republic of Germany,France, Greece, Ireland, Italy, Luxemburg, Netherlands, Portugal, Spain, United Kingdom, Austria, Finland, Sweden)

- OECD Member countries (additionally to the EC Members, Australia, Canada, Iceland, Japan, New Zealand, Norway, Switzerland, Turkey, United States of America)
- United Nations-related organisations

In 1991, the Interagency Regulatory Alternatives Group (IRAG), an ad hoc organization composed of staff from U.S. regulatory agencies, sponsored an international "Workshop on Updating Eye Irritation Test Methods: Proposals for Regulatory Consensus" to consider a number of changes in the conduct of the in vivo eye irritation test.

The U.S. regulators published their IRAG-workshop proposals in 1993 (2): An in vivo test protocol and an evaluation and classification system for the determination of eye irritation potential of chemicals was proposed. The tier scheme for testing and evaluation of the U.S. regulators (**Appendix I**) is explained in this publication in detail.

In April 1993 the German competent authority for the assessment of chemicals presented a tier scheme of the eye irritancy testing strategy at a symposium in Ottawa ("Current Trends: in vitro Skin Toxicology and Eye Irritancy Testing"). That tier scheme was worked out for the notification procedure of the European Community (**Appendix II**). The same tier scheme was presented at the "World Congress on Alternatives and Animal Use in the Life Sciences" coordinated by IRAG 1993 in Baltimore and a satellite meeting to this congress, held in Washington, DC ("Workshop on Eye Irritation Testing: Practical Applications of non-whole Animal Alternatives"). The German regulators presented their point of view and their tier scheme for the assessment of eye irritancy in a paper sent to U.S. regulators and to IRAG (3). They additionally published a tier scheme for a testing strategy for acute toxicity, corrosivity and irritancy within the report of an ECVAM (European Centre for the Validation of Alternative Methods) workshop in 1995. This tier scheme is based on the experiences of EU regulator's evaluation of test reports submitted within the EU chemicals notification procedure (4).

Through presentations and discussions at the 1991 IRAG workshop and the results of a questionnaire distributed to conference participants, it became apparent that there were areas of consensus and areas where there were different opinions as to how the test should be performed and evaluated. From these sources plus analyses conducted after the workshop, a second set of proposals was sent out for review and comment. After making changes, IRAG submitted through the U.S. Coordinator proposals to OECD (October 12, 1994) for potential additions/modifications of the 1987 OECD test guideline on eye irritancy testing. In 1995 the OECD submitted an U.S. text proposal for a revised Test Guideline 405 (Acute Eye Irritation/Corrosion).

The following proposal for the harmonization of eye irritation testing and classification considers the collection of test guidelines and classification schemes worked out by Arthur Walker (1), the OECD submission of the tier scheme of the U.S. regulators (**Appendix I**), the experiences of the German regulators basing on the EU chemicals notification procedure (3, 4) and the outcome of the "OECD Workshop on Harmonization of Validation Criteria for Alternative Tests / Harmonization and Acceptance Criteria for Alternative Toxicological Test Methods" in Solna, Sweden (22.-24. January 1996). At this meeting it was agreed on a testing strategy for eye irritation/corrosion to be included in an updated OECD Guideline 405.

REVIEW OF EXISTING GUIDELINES

This review covers the eye irritation classification schemes for chemicals which are in force in the member countries of the Organisation for Economic Cooperation and Development, OECD (5), in the European Economic Community, EU (6), the Pesticide Authorities as part of the OECD harmonization project Canadian workplace, WHMIS (7), and in the transport sectors of the United Nations, UN.

Essentially four different approaches to the evaluation of ocular hazard have been developed (**see table 1**), some of which have been used in the international regulation of chemical products [EU (6), WHMIS (7), FHSA (8), NAS (9), Kay and Calandra (10)]. The classification procedures are similar since they all are based on the rabbit eye model and utilize the Draize scoring system for ranking responses:

CORNEA (The area of corneal opacity should be noted)	
Opacity: degree of density (area most dense taken for reading)	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible	1
Easily discernible translucent area, details of iris slightly obscured	2
Nacrous area, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through the opacity	4
IRIS	
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia, or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2
CONJUNCTIVAE	
Redness (refers to palpebral and bulbar conjunctivae, cornea and iris)	
Blood vessels normal	0
Some blood vessels definitely hyperaemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3
Chemosis: lids and/or nictating membranes	
No swelling	0
Any swelling above normal (includes nictating membranes)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

The scores are processed differently to decide if a test substance is irritant or not and/or to grade the severity of the irritation. In addition, the following features are of varying importance in each classification scheme (11):

- the intensity of the irritant response in different regions of the anterior eye

- the "weighting" of response scores prior to determining an irritation index
- the level of response during the first three days after exposure
- the reversibility or irreversibility of a response

Additionally, there are differences in the number of animals required per test, and in the way in which the effects, or the number of animals exhibiting effects, are interpreted in order to determine whether the test substance is an irritant.

Since none of the current evaluation systems consider data from irrigation studies, it is proposed that such studies should be conducted unless there is a scientific justification.

Table 1: International Evaluation and Classification Systems

Methodology	FHSA	NAS	Modified EEC	EEC
	CPSC., FDA OSHA	EPA	CANADA	EEC
Number of animals:				
Screen for severe (Vol.)	--	--	--	1 (0.1 ml)
Main Test	6 (12, 18)	6	6	≥ 3
Scoring times	1, 2, 3 d	any ≤ 21 d	1 hr; 1, 2, 3 d	1, 2, 3 d
Minimal positive response:				
Corneal opacity	1	1	2*	2**
Iritis	1	1	1*	1**
Conjuctival				
redness	2	2	2,5*	2,5**
chemosis	2	2	2,5*	2**
Positive test	≥ 4 positive	≥ 1 positive	*mean of	≥ 2 positive
	of 6 animals	of 6 animals	6 animals	of 3 animals
Number of classes:				
Irritant	1	3	1	2
Corrosive	1	1	--	--
Severe irritant class				
when either				
(a) corneal opacity				≥ 3**
(b) iritis				2**
or (c)				Positive scores have not cleared on day 21

* mean of 6 animals

** mean of 3 scoring times

To be included in Revised Step 1 for Harmonization of Eye Irritation/Corrosion (Page 6)

EU guideline (6)

Generally a Draize eye test is performed using 1 animal (if severe effects are suspected) or 3 animals (if no severe eye irritation is anticipated). Ocular lesions which occur within 72 hr after exposure and which persist for at least 24 hr after instillation qualify a material to be classified as irritant to the eye, if they reach certain score levels and times of duration. Two levels of irritancy are recognised by the assignanation of different risk phrases:

Risk phrase	Ocular lesions
R 36: Irritating to eyes	significant but reversible
R 41: Risk of serious damage to eyes	severe and/or irreversible

Criteria for classification: mean scores

	R 36	R 41
corneal opacity	≥ 2, < 3 *	≥ 3 *
iris lesion	≥ 1, < 1.5 *	≥ 1.5 *
redness of the conjunctivae	≥ 2.5 *	
oedema of the conjunctivae	≥ 2 *	
(chemosis)		

* If the test has been carried out using 3 animals and the lesions on 2 or more animals are equivalent to any of the above values

Other observations (e.g., lacrimation, signs of pain) at each of the reading times (24, 48 and 72 hr) should be considered in the evaluation of test response.

Criteria for classification: duration of effects

The duration of the study should be sufficient to evaluate fully the reversibility or irreversibility of the effects observed. Extended observation may be necessary if there is persistent corneal involvement or other ocular irritation in any animal in order to determine the progress of the lesions.

Persistent substance causing colouration of the eye (this effect demonstrating irre- versible penetration of the chemical into the cells of the eye) and irreversible corneal opacity are also judged as severe eye damage because these effects diminish crucially the function of the eye as an optical organ.
Animals showing severe and enduring signs of distress and pain may need to be humanely killed. In that case the substance has to be labelled R 41 without taking into account the question of possible reversibility of effects.

Test methods: references to Annex V (6) or OECD (5) methods, including structure-activity considerations and animal-free alternative methods.

Canada, occupational regulations (7)

A pure substance or tested mixture falls into Subdivision B of Division 2 of Class D - Poisonous and Infectious Material - if, in an animal assay,

mean corneal damage grade	2 or more
mean iris damage grade	1 or more
mean conjunctival redness/damage grade	2.5 or more

when tested in accordance with OECD Test Guideline No. 405 (5) is measured at any of the times specified in the test; the means are calculated from the grades of all the animals at a given scoring time. The OECD method for eye irritation assessment uses at least 3 rabbits.

Japan (12)

Japan does not have clearly defined definitions or criteria for classification as irritant to the eye. But one of the criteria of definition for ”Poisonous and Deleterious Sub-stances” in Japan takes into account irritating effects:

Irritation to skin and mucous membranes - Deleterious substance: substances which have similar or more irritation than sulphuric acid, sodium hydroxide, phenol etc.

Test methods: not specified

Norway (13)

Definitions:

Corrosive: all substances which by contact in small doses with living tissue (skin, mucous membranes) destroy the tissue and leave a sore

Irritant: all substances which by contact in small doses with skin or mucous membranes result in symptomes such as redness, blisters, swelling, scorching and the like

Classification:

Category	Class of hazard	Code
Corrosive	Hazardous to health	C
Irritant	Hazardous to health	Xi

Switzerland (14)

Switzerland does not have clearly defined definitions or criteria for classification as irritant to the eye. The Federal Law on Trade in Toxic Substances classifies sub- stances into five toxicity categories on the basis of acute oral lethal dose. There is no specific classification based on corrosion, irritation, or skin sensitisation.

However, in addition to the LD50 data, "the Federal Office shall also take into consideration, where known, or shall require from the registrant in justifiable cases: ...

(c) data concerning the danger that the toxic substance presentsthrough an irritant or corrosive effect on skin and mucous membrane

Classification criteria: not specified
Test methods: not specified

United States of America

Federal Hazardous Substances Act method (15)

Definitions:
Corrosive: a chemical that causes visible destruction of, or irreversible alterations in, living tissue by chemical action at the site of contact.

Irritant: a chemical, which is not corrosive, but which causes a reversible inflammatory effect on living tissue by chemical action at the site of contact. A chemical is an eye irritant if so determined under the procedure listed in:

Evaluation criteria:
Eye irritation (method CFR 1500.42: Federal Hazardous Substances Act Regulations under the Consumer Product Safety Commission, the Occupational Safety and Health Administration and under Food and Drug Administration policy): At least 6 rabbits are used, grades of ocular reaction are recorded 24, 48 and 72 hr after instillation. An animal shall be considered as exhibiting a positive reaction if the test substance produces at any time cornea $\geq$1, iris $\geq$1, redness $\geq$2, chemosis $\geq$2:

Positive reaction in 4 or more animals:	test positive
Positive reaction in only one animal:	test negative
Positive reaction in 2 or 3 animals:	repeat test on a further group of 6 animals:

- positive reaction in 3 or more animals: test positive
- positive reaction in 1 or 2 animals: repeat test on a third group of different animals: if any animal gives a positive response the test substance will be regarded as an irritant

U. S. National Academy of Sciences method (16)

Definitions:
Corrosive: a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application.....tests should be applied when contact of the substance with other than skin tissue is being considered.
Irritant: any (not corrosive) substance which on immediate, prolonged, or repeated contact with normal living tissue will induce a local inflammatory reaction

This method, used by the U. S. Environmental Protection Agency pesticide program employs 6 animals. Animals are scored at any time up to 21 days. The maximum score in an animal is used for classification. A test is positive if one tested animal has a grade of cornea ≥1, iris ≥1, redness ≥2, chemosis ≥2. There are 4 hazard classes, depending upon when lesions reverse:

Toxicity category	Criteria	Label
category 4	essentially inconsequential effects	caution
category 3	effects reversible within 7 days	caution
category 2	effects reversible within 21 days	warning
category 1	effects not reversible in 21 days (corrosive)	danger

United Nations-related Organisations

Only dermal corrosivity is taken into account, eye corrosivity or eye irritating properties are not considered dangerous properties within the "Orange Book" (17).

MODIFICATIONS TO THE 1987 OECD EYE IRRITATION TEST GUIDELINE, PROPOSED IN 1994 BY IRAG

In December 1993 the Interagency Regulatory Alternatives Group (IRAG), an ad hoc organisation composed of staff from U.S. regulatory agencies, sent out a proposal for modifications to the 1987 OECD eye irritation test guideline that based on the outcome of two IRAG meetings and analyses conducted after a workshop on updating eye irritation test methods. After an international discussion of their proposals, IRAG submitted through the U.S. Coordinator revised proposals to OECD (October 12, 1994) for potential additions/modifications of the 1987 OECD test guideline on eye irritancy testing. A tier scheme for eye irritation testing to be annexed to the updated OECD guideline was worked out (**Appendix I**).

The objective of the proposals was to establish a tier testing process, to diminish the number of materials needing any animal testing, to decrease the number of animals per test, to minimize animal distress, to decrease ancillary testing and to ensure development of information that will be suitable for hazard classification.

The IRAG tier testing process starts with initial considerations before commencing animal testing on a chemical. Data on whichever of the following 5 parameters is to be reviewed:

- physocochemical properties including pH extremes, (usually about ≤ 2 or ≥ 11.5) and the use of potential buffering capacity information,
- severe dermal irritation or corrosivity,
- validated and accepted non-whole animal (e.g., in vitro) alternatives,
- structure-activity relationships (SAR), that is, testing data and historical experience on structurally related chemicals (e.g., organic peroxides) and mixtures,
- human experience.

A sixth parameter, acute dermal toxicity, is also important to consider because any agent that is acutely very toxic via the dermal route should be kept away from the surface of the body, including the eye. The IRAG tier scheme draft outlined in **Appendix I** was worked out as a basis for elaboration of a final tier scheme to be incorporated in an OECD guideline. At the "OECD Workshop on Harmonization of Validation Ctriteria for Alternative Tests / Harmonization and Acceptance Criteria for Alternative Toxicological Test Methods" in Solna, Sweden (22.-24. January 1996) the international delegates integrated the IRAG tier scheme and the German tier scheme worked out for the EU (**Appendix II**) into one joint proposal for a testing strategy to be included in Guideline 405 (see OECD tier scheme in chapter **5.**).

RESULTS OF EVALUATION OF EYE IRRITANCY TEST DATA SUBMITTED WITHIN THE EUROPEAN UNION

Though basing on the same animal test and on the same scoring system, there is a remarkable disparity in eye irritation classification across internationally used systems (**see table 2**):

Table 2: Comparison of classification decisions* (IRAG workshop 1991)

		% Irritant		
	EPA	FHSA	EU	
EPA chemicals (N = 56)	79	66	30	
CPSC/FDA chemicals (N = 50)	88	66	14	
ECETOC (1988) chemicals (N = 70)		57	26 **	

* A test was positive when $\geq$ 4 of 6 animals were positive, except for EPA where $\geq$ 1 of 6 animals was positive. The EU (3-animal test) considers $\geq$2 of 3 positive animals as a positive test; thus the use of $\geq$ 4 positive of 6 animals here preserves the same proportion positive.

** For an EU (1987) 6-animal test, animal scores are averaged at days 1, 2 and 3 and across all 6 animals in determining whether the criteria for a positive test have been met.

In addition to the problems with eye irritation classification across internationally used systems, there are problems resulting from questions like

- whether and in what cases there exist relationships between skin and eye irritating properties of chemical substances (section 4.1),

- assessment of the probable healing time for eye damage or eye irritation effects (section 4.1.5).

These questions are more or less subject of scientific considerations. Therefore Draize test data submitted to the national competent authorities of the EU were evaluated in Germany in order to clarify these questions.

Relationships between skin and eye irritation

The evidence of this relationship can only be judged in connection with considerations on the evaluation philosophy and the evaluation criteria for skin and eye irritation/corrosion used. These criteria reflect not only mere local irritant effects of chemical agents in different biological tissues, they reflect as well the ethical esteem of the functional entirety of the organs skin and eye and the aims of the respective hazard classification. It is necessary to point out that "eye irritation/corrosion" includes also effects like pannus formation, corneal opacity, loss of visual sight or irreversible discolouration of iris and/or cornea - effects that are not signs of irritancy but significantly disturb the optical function of the eye as an organ. It is also necessary to point out that nearly 95% of the industrial chemicals produce some kind of eye irritancy. Neither is there a sense in making classification differences between different kinds of serious damage to eyes resulting e.g. from severe eye irritation/corrosion or from irreversible corneal opacity; nor is there a sense in classifying 95% of all chemical agents as "irritants".

Hazard assessment philosophy as well as hazard assessment criteria are expressed through the respective classification systems based on calculations with "scores" - a method which translates subjective toxicological observations into objective calculable numbers. All classification systems use the grading system according to Draize; but they compute hazard assessment results for classification of the observed response in different ways:

The classification system used in U.S. guidelines (corneal opacity of 1 or above, iritis of 1 or above, conjunctival redness/chemosis of 2 or above) results in most cases in labelling of substances for eye irritating properties that are labelled for their skin irritating properties as well as stated by regulators of U.S. organisations (2). The classification system of the EU on the other hand (corneal opacity of 2 or above, iritis of 1 or above, conjunctival redness of 2.5 or above, conjunctival swelling of 2 or above) does not construct a relationship between skin and eye irritation.

Two sets of evaluations have been conducted to investigate the relationships between skin irritation and corrosion and eye irritancy. The first is a review of data bases by the United States; the second is one conducted in Germany. Many published papers summarized in Hurley et al. (18) have indicated that a sizable proportion of test materials producing significant dermal reactions are likely to produce some degree of ocular irritation. From the testing of about 600 chemicals from three sources, about 75% of the moderately irritating to corrosive materials on the skin were irritating to the eye. Lesser dermal reactions were not correlated with ocular effects. These findings support the use of moderately severe and severe dermal effects to predict potential reactions in the eye.

The second evaluation involved 742 new chemicals submitted as part of the notification procedure of the EU, 221 New Chemicals were found demonstrating skin and/or eye irritant/corrosive properties that have to be labelled corresponding to EU labeling guidelines. 186 (25 %) of the 742 notified substances fulfill the EU criteria for relevant eye irritation or eye corrosion. In the EU there is no differenciation between "irritancy" and "severe irritancy," but with respect to "irritancy" and "serious damage" (**see table 3**).

Table 3: Irritant/corrosive properties of the mentioned 221 substances:

local irritation/ corrosion effects	symbol of danger	risk phrase	number of substance
corrosive to skin	C: Corrosive	R 35 R 34	5 43
irritating to skin and eyes	Xi: Irritant	R 38/41 R 36/38	18 10
reversible skin irritation (eye irritation irrelevant)	Xi: Irritant	R 38	35
reversible eye irritation (skin irritation irrelevant)	Xi: Irritant	R 36	26
persistent eye irritation/damage (skin irritation irrelevant)	Xi: Irritant	R 41	84
			Total: 221

"irritation irrelevant" stands for no irritancy or for irritating effects that are not to be labelled according to EU criteria.

Skin corrosive substances

48 Substances (i.e. 6.5 % of all 742 chemicals) are labelled as corrosive to skin. Due to ethical reasons, data on eye irritation are usually not assessed for skin corrosive substances.

a) For the 5 substances labelled as R 35 (causes severe burns) no eye irritation test was conducted
b) For 17 out of the 43 substances labelled as R 34 (causes burns) an eye irritancy test was conducted, demonstrating the following lesions:
   - 10 substances caused severe irreversible eye damage,
   - 3 substances caused mild or moderate eye irritation for more than 10 days,
   - 4 skin corrosive substances caused only marginal conjunctival irritation

Substances showing significant local irritancy to skin and eyes

28 Substances (i.e. 3.8 % of all 742 chemicals) are labelled as irritating to skin and eyes:

a) 18 of the skin irritating substances (R 38: Irritating to skin) are labelled also R 41 for causing serious damage to eyes
b) 10 of the skin irritating substances (R 38: Irritating to skin) are labelled also R 36 (irritating to eyes) for significant but reversible eye irritating properties

Substances showing only significant local irritancy to skin

A total of 63 substances labelled as R 38 (irritating to skin) was detected. Out of these, 35 substances (i.e. 4.7 % of all 742 chemicals, but 55.6 % of all 63 skin irritants) are labelled only because of their skin irritant properties. Six of the R 38-labelled chemicals showed only slight conjunctival irritation healing within 24 hours.

Substances showing only significant local irritancy to eyes

110 substances (i.e. 14.8 % of all 742 chemicals) are labelled only because of their eye irritant or eye damaging properties. 48 of them do not exhibit any skin irritation effect at all [16 out of the 36 reversibly irritating chemicals (R 36) and 32 out of the 84 chemicals causing severe eye damage (R 41)].

Duration and severity of eye irritation effects

Out of the 742 chemical substances of the German regulator's data evaluation, 556 are not labelled as eye irritants according to the EU legislation. These substances exhibited the following mild effects:

- Only 29 substances (3.9 % of all 742 chemicals) did not exhibit any irritation to eyes of rabbits.

- 88 substances (11.9 %) demonstrated eye irritancy reversible within one day.

- The great majority of the substances (379 substances or 51.1 %) caused mild local eye irritant effects reversible within 2-7 days.

For chemicals labelled on the basis of their eye irritating/damaging properties, the EU data evaluation gave the following results:

a) Substances labelled as R 36: 36 of all 742 substances are labelled R 36 (irritating to eyes) or R 36/38 (Irritating to eyes and skin). Corresponding to EU legislation these substances exhibit moderate/strong eye irritation reversible within 21 days.

b) Substances labelled as R 41: 102 of all 742 substances are labelled R 41 (risk of serious damage to eyes) or R 38/41. All of these substances exhibit eye lesions not reversible within 21 days:
   - 8 substances are labelled as R 41 based on theoretical considerations (mostly extreme pH values); no animal test was conducted
   - 70 substances are labelled as R 41 because of severe irreversible eye damage (32 of them did not exhibit any irritation to skin)
   - 24 substances are labelled as R 41 because of minor irreversible eye effects (12 of these substances additionally cause other strong (but reversible) eye irritant effects, 12 substances are labelled with R 41 exclusively because of the persistence of minor eye irritant effects)

   The possibility to differentiate between hazardous and less hazardous substances depends strongly on the classification system used for the evaluation of eye lesions and on the decisions made with reference to reversibility/irreversibility of effects within fixed observation times.

Possibility of reducing the number of test animals

Based on experience with eye irritation tests according to the EU notification proce- dure it was detected that using a one-animal limit test followed by testing of additional rabbits, if necessary, may be the most appropriate strategy. It was found that

- the degree of irritancy is similar for all animals when testing substances with strong irritating properties. In these cases testing with one animal is sufficient.

- in tests with substances without relevant irritating potency none of the animals exhibits significant effects or suffers relevantly.

- testing mild or moderate effects leads to ambiguous results with all methods. Even animal tests using 18 rabbits will not result in a clear-cut decision. Therefore labelling borderline eye irritancy is a question of toxicologic hazard assessment considerations (expert judgement) and not a question of the number of animals used within a test.

Termination of animals on test, minimal observation time

Animals with severe lesions or indications of undue stress should be sacrificed; a rationale should accompany the decision; and the implications of the lesion for evaluating the animal and test outcome should be provided. Animals can be removed from a test whenever information allows for the classification of the test material. Classification systems commonly evaluate lesions at 24, 48 and 72 hours after treatment. If lesions have reversed by that time or are severe and indicative of irreversible responses (e.g., cornea grade 4), the chemical can be evaluated and classified. Animals with lesions at 72 hours should be continued on test and observed regularly (at least on days 7, 14 and 21) until lesions reverse or up to a maximum of 21 days when the test ends.

Termination of a test after 72 hours is only appropriate for the assessment of eye lesions healing within this time period. As to healing of corneal opacity or conjunctival redness still apparent after 3 days, German regulators made the following experiences:

- Most of the relevant but weak conjunctival leasons heal between days 7 and 14 after application.

- Corneal opacity grade 2 normally is healing after an observation period of more than 10 days or is still apparent on day 21.

- Corneal opacity grade 4 results in irreversible damage.

Thus, after a 7 day observation period (as was discussed within the EU) it is not possible to decide whether conjunctival leasons or corneal opacity will disappear or will be persistent. The minimal observation time for such decisions is 14 days.

Eye irritancy testing strategy for New Chemicals within the notification procedure of the European Community

Based on the reported data evaluations and on other experiences made within the notification procedure for New Substances of the EU and additionally based on the experiences of the German Centre for Development and Validation of Animal Alter- natives (ZEBET) as to standardization of alternative tests, evaluation of in vitro test data and in vivo / in vitro data correlations, the German regulators drafted an ”Eye Irritancy Testing Strategy for New Chemicals within the Notification Procedure of the European Community” presented by Eva Schlede at the November 1993 World Con-gress in Baltimore (**Appendix II**):

Step 1: Measurement of pH:
Eye irritancy properties of strongly acidic (pH $\leq$ 2) or alkaline substances (pH $\leq$ 11,5) need not be tested because of their probable corrosive properties. Buffer capa- city should also be taken into account. The fact that some strong acidic or even some strong alkaline substances may exhibit only slight effects to skin or eye tissues is to be neglected because of ethical considerations.

Step 2: Evaluation of skin corrosivity/irritancy
Eye irritant properties of substances corrosive to skin need not be tested though a number of skin corrosive substances demonstrate only mild eye irritation (s. chapter **4.1**). The decision not to conduct eye irritation testing of skin corrosive substances is an ethical decision.

Step 3: Structure-activity-relationships considerations;
Theoretical considerations on qualitative structure-activity-relationships as ”guidan- ce information” or computational chemical modelling to predict eye irritant properties by means of SAR-Models or such considerations combined with ...

Step 4: In vitro methods or other alternative tests
... results of validated alternative methods predicting serious eye irritant/corrosive effects to eyes may be sufficient for labelling the substances with ”R 41 (Risk of serious damage to eyes”

Step 5: Draize eye test with one animal
In case of results showing severe irritant/corrosive effects no further testing is required. The substance is labelled with ”R 41 (Risk of serious damage to eyes)”.

Step 6: Draize eye test with two additional animals

The EU prodecure including in vitro test methods is already used for regulatory purposes in some of the EU member states. There are, however, differences as far as in vitro assays are concerned which are being accepted by the national compe- tent authorities. This is due to differences in experience with specific in vitro assays at the national level. Taking into account from the German validation trial (19), the HET-CAM test is accepted as an in vitro alternative to the Draize eye test by Geman regulators for predicting serious damage to the eye that requires labelling with the risk-phrase ”R 41 (risk of serious damage to eyes)”. At the same time in France and Belgium the national competent authorities are accepting in vitro data obtained with the BCOP assay (20) and regulatory authorities in the U.K. are accepting data obtained with the isolated rabbit eye assay. The results with all these alternative methods are solely used to label a substance as “R 41 (risk of serious damage to eyes)“.

RESULTS OF EYE IRRITATION COMPARISONS WORKED OUT BY US REGULATORS

A comparison was made of the sensitivity of different existing ocular irritation/corrosion classification systems. A database of 140 chemicals and products was assembled to make these evaluations, comprised of the following sources:

ECETOC industrial chemicals	17.1%	(24/140)
EPA pesticide active ingredients	42.9%	(60/140)
EPA pesticide products	12.9%	(18/140)
EPA new industrial chemicals	19.3%	(27/140)
German new industrial chemicals	7.9%	(11/140)

Using these data, the total proportion of materials positive for irritation or corrosion according to existing classification systems include: EPA pesticides 88.5%, FHSA (used by the US Consumer Product Safety Commission and Food and Drug Administration) 78.3%, Canada workplace 47.2% and EU 44.3% (**Table 4**).

Table 4. Percent of test materials positive for ocular effects using current classification systems

Database	EU R36	EU R41	EPA Cat I	EPA Cat. II	EPA Cat. III	FHSA	Canada w
EPA p (n=82)	17.1% (14/82)	23.2% (19/82)	30.4% (24/79)	27.8% (22/79)	25.3% (20/79)	79.2% (57/72)	47.6% (39/82)
EPA i (n=27)	33.3% (9/27)	7.4% (2/27)	7.4% (2/27)	37.0% (10/27)	55.6% (15/27)	84.2% (16/19)	44.4% (12/27)
ECETOC (n=24)	20.0% (4/20)	15.0% (3/20)	13.6% (3/22)	31.8% (7/22)	40.9% (9/22)	66.7% (10/15)	45.8% (11/24)
German (n=11)	54.5% (6/11)	45.5% (5/11)	45.5% (5/11)	27.3% (3/11)	27.3% (3/11)	N/A	54.5% (6/11)
Summary (n=144)	**23.6% (33/140)**	**20.7% (29/140)**	**24.5% (34/139)**	**30.2% (42/139)**	**33.8% (47/139)**	**78.3% (83/106)**	**47.2% (68/144)**

Canada w -- Canada workplace
EPA p -- EPA pesticides
EPA i -- EPA industrial chemicals

In an analysis using a different database, the reasons for the disparitiy in percent of test materials that are irritants in the EU and US (FHSA) systems were analyzed. The two major differences between the two systems are that an animal is positive under FHSA if it has a positive lesion at any scoring time, whereas in the EU an animal is positive if the mean of three scoring periods is positive. In addition, the US calls a cornea 1 lesion as positive, while the EU calls for a cornea 2 lesion; the US also uses a conjunctival redness of 2, while the EU uses 2.5. In the analysis, 65% of test materials were positive under FHSA, and 34% were positive under the EU system. Test materials were also scored using the US values (cornea 1, redness 2), but with averaging scores over three grading periods; in this case 47% of materials were positive. This shows that the lesion score differences and averaging of responses contribute nearly equally to the difference between the EU and US systems.

Some authorities, namely the pesticide programs in Canada and the US use multiple hazard classification descriptors to guide in the determination of protective clothing and other considerations. One important determinant in ocular lesions concerns the time of reversal. To evaluate the potential reversibility of ocular lesions, EPA pesticide and industrial chemicals were reviewed. Only animals that were carried until the end of the test were used. Opacity and iritis are clear when the scores return to 0. Redness and chemosis are clear when the scores return to 1 or 0. A score of 1 or 0 are considered clear for redness and chemosis. **Table 5** shows that time to reversibility is a function of the severity of the ocular lesions. With the most common, minimal lesions (cornea 1, iris 1, redness 2, edema 2), about 60% or more have reversed by day 7 of observation. Such information could be used in selecting potential subclasses of irritants.

A potential harmonized proposal was investigated that addresses a number of the issues that have been discussed above. The proposal includes use of the US positive scores (cornea 1, redness 2) along with iris 1 and edema 2. It also requires the averaging of responses across 3 grading periods. Lastly, it embodies the use of optimal subclasses that differ as to the time of reversibility of lesions. The details of the proposal are as follows:

Table 5. Reversibility of ocular lesions over time

Response	Grade on day 1	Number of animals	Percentage not cleared by day			
			3	7	14	21
Cornea	1	157	71	41	27	22
	2	45	89	67	40	40
	3	10	100	100	100	100
	4	12	92	92	92	92
Iris	1	199	61	29	15	7
	2	11	82	36	27	27
Redness	2	223	54	13	4	3
	3	88	87	35	8	6
Chemosis	2	155	31	9	2	1
	3	84	81	37	13	7
	4	40	95	68	30	23

OECD OCULAR PROPOSAL (January 1998)

The proposed procedure is a 3 animal, 3 day test, extended to 21 days to determine reversibility.

Category A (irritating to eyes)

The eyes are scored on days 1, 2, and 3. An animal is positive if the mean score for days 1, 2 and 3 is any of the following:

opacity $\geq$ 1.0
iritis $\geq$ 1.0
redness $\geq$2.0
chemosis $\geq$ 2.0

Thus, an animal mean score is positive if:
opacity = 1, 2, 3 or 4
iritis = 1 or 2
redness = 2 or 3
chemosis = 2, 3 or 4

A test material is classed as an irritant when 2/3 (4/6) of animals have a positive mean score. Category A can be broken down into 2 sub-categories.

Category A1

The criteria for Category A must first be met. Then, if all animals clear by day 7, a classification of A1 is given.

Category A2

The criteria for Category A must first be met. Then, if any animals are still positive on day 7, but clear by day 21, a classification of A2 is given.

Clear means:

opacity = 0
iritis = 0
redness = 0 or 1
chemosis = 0 or 1

Category B (irreversible effects on the eye)

A test material demonstrates irreversible effects if either of the following three criteria are met:

(1) Category B classification requires that 1/3 (2/6) animals meet any of the following criteria:
A mean score for days 1, 2, and 3 of:
opacity > 3.0
iritis > 1.5

(2) Category B classification is also given if at day 21, 1/3 (2/6) animals meet any of the following criteria:
opacity $\geq$ 1
iritis $\geq$ 1
redness $\geq$ 1
chemosis $\geq$ 1
discoloration of the cornea by a dye substance
adhesion
pannus

(3) Category B classification is also given if a grade 4 opacity or destruction of the cornea occurs at any time during the test in at least 1 animal.

Using the same databases as in Table 1, the proposed hazard classification was evaluated as to its sensitivities. Overall, about 30 % of test materials induce irritating effects, while about 27% induce irreversible effects, for a total of about 57% positive materials (**Table 6**). The optional subcategories based on time of reversal of lesions, results in 8% being designated as Category A1 (reversing in 7 days) and 22% as Category A2 (reversing between 7 and 21 days). The sensitivity of the proposed system is also compared with the existing systems in **Table 7.**

The proposed system classifies 57% of test materials as positive for ocular effects in contrast to 44% for the EU, 89% for EPA pesticides, 78% for FHSA and 47% for Canada workplace.

Table 6. Percent (proportion) of chemicals/products with irritating or irreversible ocular effects for the proposed classification system (January 1998)

Database	Irritating Effects			Irreversible Effects	Total Effects
	CategoryA1(clear < D7)	**CategoryA2(clear ≥ D7)**	**Category A (combined)**	**Category B**	**Combined A+B**
EPA p (n=82)	6.10% (5/82)	17.1% (14/82)	23.2% (19/82)	32.9% (27/82)	56.1% (46/82)
EPA i (n= 27)	7.4% (2/27)	25.9% (7/27)	33.3% (9/27)	14.8% (4/27)	48.1% (13/27)
ECETOC (n=23)	8.7% (2/23)	30.4% (7/23)	39.1% (9/23)	13.0% (3/23)	52.2% (12/23)
German (n=11)	27.3% (3/11)	27.3% (3/11)	54.5% (6/11)	45.5% (5/11)	100% (11/11)
Summary (n=143)	**8.4% (12/143)**	**21.7% (31/143)**	**30.1% (43/143)**	**27.3% (39/143)**	**57.3% (82/143)**

D -- day of observation
EPA i -- EPA industrial chemicals
EPA p -- EPA pesticides

Table 7. Comparison of percent positive test materials under existing and the proposed (January 1998) classification systems

Existing		Proposed				
System	Current	Category A1	Category A2	Category A	Category B	Category A + B
EU R41	20.7%				27.3%	
EU R36	23.6%			30.1%		
EPA Cat.I	24.5%				27.3%	
EPA Cat.II	30.2%		21.7%			
EPA Cat.III	33.8%	8.4%				
FHSA	78.3%					57.3%
Canada work	47.2%					57.3%

Notes to Tables 4-7

1. Tests with 4 and 5 animals were treated as 6-animal tests.

2. Tests with 1 and 2 animals were treated as 3-animal tests.

3. Tests that could not be classified under a particular system were dropped for that system only. For example, in Table 5 the total number of tests in the ECETOC database was 24. 20 could be classified under the EU system, 22 under EPA, 15 under FHSA, and all 24 under Canada workplace.

4. In Table 4, the ECETOC database has a "n" of 23. Test-00235, using the OECD January 1998 criteria had 3 positive animals out of 4 and therefore could not be classified.

5. In Table 5 EPA Pesticides database, 3 tests could not be classified under EPA criteria. Tests 00084, 00087, 00096 were all 3-animal tests with no positive animals. EPA requires only 1 positive animal out of 6 for a positive test. Under the EPA criteria, a test must have at least 6 animals which are all negative for a classification of Cat. 4 (non-irritant).

6. In Table 5 EPA Pesticides database, 10 tests could not be classified under FHSA criteria. Tests 00084, 00087, 00096, 00108 were all 3-animal tests. 3-animal tests can't be classified under FHSA. FHSA requires at least 4 positive animals out of 6 for a positive test. Test-00064 had 2 positive animals out of 4. The addition of two more animals could result in either a positive or inconclusive test. Tests 00093, 00105, 00106 had 2 positive animals out of 6 and tests 00117 and 00121 had 3 positive animals out of 6 which under FHSA are inconclusive results.

7. In Table 5 EPA industrial chemical database, 8 tests could not be classified under FHSA. Tests 00131, 00134, 00143, 00146, 00150, 00162, 00163 were all 3-animal tests. Test-00145 had 2 positive animals out of 6 and was inconclusive.

8. In Table 5 ECETOC database, 4 tests could not be classified under the EU system. These were all 4-animal tests. Test 00235 had 2 positive animals and tests 00229, 00236, 00242 had 3 positive animals. In all cases, the addition of two more animals could result in either a positive or negative test.

9. In Table 5 ECETOC database, 2 tests could not be classified under the EPA system. Test-00245 was a 3-animal test and test-00246 was a 4-animal test. Both tests had 0 positive animals.

10. In Table 5 ECETOC database, 9 tests could not be classified under FHSA. Tests 00232 and 00243 were 1-animal tests. Tests 00228, 00240, and 00245 were 3-animal tests. Test 00225 had 2 positive animals out of 4 and test 00227 had 3 positive animals out of 4. With the addition of two more animals, both tests could be either positive or inconclusive. Test 00246 had 0 positive animals out of 4 and with the addition two more animals would be either negative or inconclusive. Test-00230 had 3 positive animals out of 6 and was inconclusive.

11. In Table 5 German database, the tests could not be classified under FHSA because they were all 3-animal tests.

12. The data was made up of 140 products and 144 tests (4 repeat tests).

13. Of the 39 Category B classifications, 7.7% (3/39) qualified without first meeting the Category A requirement (at least 2/3 or 4/6 positive animals).

14. The number of animals per test is as follows:

1-animal tests:	1.4%	(2/144)
2-animal tests:	0%	
3-animal tests:	17.4%	(25/144)
4-animal tests:	9.0%	(13/144)
5-animal tests:	1.4%	(2/144)
6-animal tests:	69.4%	(100/144)

9-animal tests: 0.7% (1/144)
12-animal tests: 0.7% (1/144)

15. Criteria contributing to Category B classification.

	Irritation on day 21	**Opacity = 4**	**Opacity > 3**	**Iritis > 1.5**
Irritation on day 21	25.6% (10/39) (2/6,2/6, 4/6,5/6,6/6,1/3, 1/3, 1/3, 3/3, 3/3)			5.1% (2/39) (3/3 1/3 5/6 2/6)
Opacity = 4	23.1% (9/39) (1/1 1/1, 1/1 1/1 5/6 4/6, 4/6 6/6 6/6 6/6, 1/6 4/6 3/3 3/3, 3/6 6/6 1/6 2/6)	20.5% (8/39) (1/6, 1/6, 1/6, 1/6, 2/6, 6/6, 6/6, 1/9)		
Opacity > 3		5.1% (2/39) (2/6 2/6 2/6 2/6)	0% (0/39)	
Iritis > 1.5				7.7% (3/39) (2/5, 5/5, 6/6)
Opacity > 3 and Opacity = 4	5.1% (2/39) (2/6 *3/6* 4/6 2/6 *3/6* 3/6)			2.6% (1/39) (6/6 *6/6* 6/6)

One test met all of the criteria for Category B in 6/6 animals. One test had rupture of the cornea in 6/6 animals.

SUMMARY OF EYE IRRITATION CLASSIFICATION SYSTEMS

FHSA

The FHSA procedure is a 6 animal, 3 day, 3-tiered procedure. This test requires only an Irritant/Non-Irritant classification. Severity of response is not determined. The eyes are scored on days 1, 2, and 3. An animal is positive if any of the following occurs at any of the grading periods:

opacity ≥ 1
iritis ≥ 1
redness ≥ 2
chemosis ≥ 2.

A classification of Irritant requires 4 or more positive animals. If only 1 animal is positive, the product is classified as a Non-Irritant.

If 2 or 3 animals are positive, the test is repeated with 6 additional animals. If in the second test 3 or more animals are positive, the product is an Irritant.

If only 1 or 2 animals are positive in the second test, the test is repeated with an additional 6 animals.

If 1 animal is positive in the third test, the product is an Irritant.

EPA

The EPA procedure is a 6 animal, 21 day procedure. The eyes are scored at 1 hr., 1, 2, 3, 7, 14, 21 days. An animal is positive if any of the following occurs at any of the grading periods:

opacity ≥ 1
iritis ≥ 1
redness ≥ 2
chemosis ≥ 2.

Placement in an irritant category requires 1 or more positive animals.

Cat I: Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than21 days.
Cat II: Corneal involvement or irritation clearing in 8-21 days.
Cat III: Corneal involvement or irritation clearing in 7 days or less.
Cat IV: Minimal effects clearing in less than 24 hours.

EU

The EU procedure is a 3 animal, 3 day test with an extension to day 21 to determine severity. The eyes are scored on day 1, 2, and 3. If necessary, the animal is kept until day 21 to determine severity of response (Irritant or Serious). An animal is positive if the **average** score for days 1, 2, and 3 is any of the following:

opacity ≥ 2
iritis ≥ 1
redness ≥ 2.5
chemosis ≥ 2.

A classification of Irritant requires 2/3 (4/6) positive animals.

A classification of Serious Irritant requires that 2/3 (4/6) animals meet any of the following criteria:

An average score for days 1-3 of:
opacity ≥ 3
iritis ≥ 1.5.

A classification of Serious Irritant is also given if at day 21 1/3 (2/6) animals meet any of the following criteria:

opacity ≥ 1
iritis ≥ 1
redness ≥ 1
chemosis ≥ 1.

CANADA PESTICIDES

Use Draize 1944 scoring. For formulation can also use Kay & Calandra (1962).

0-0.5 Non-irritant
0.5-2.5 Practically Non-irritant
2.5-15.0 Minimal Irritant
15.0-25.0 Mild Irritant
25.0-50.0 Moderate Irritant
50.0-80.0 Severe Irritant
80.0-110.0 Extremely Severe Irritant

CANADA WORKPLACE

Use OECD test guidelines (405) dated 5/12/81
The eyes are scored at 1 hr., 1, 2, 3 days.
Across animals calculate

Average opacity for each day
Average iritis for each day
Average redness for each day
Average chemosis for each day

Irritant if the average score at any of the grading times is any of the following:

Cornea ≥ 2.0
Iris ≥ 1.0
Redness ≥ 2.5
Chemosis ≥ 2.5

Example:		1 hr.	1 d	2 d	3 d
	Opacity	1.0	**2.5**	1.5	1.0
	Iritis	0.0	0.0	0.0	0.0
	Redness	1.5	2.0	2.0	2.0
	Chemosis	1.5	1.5	1.5	1.5

This product would be classified as an irritant because of the average of 2.5 for opacity at day 1.

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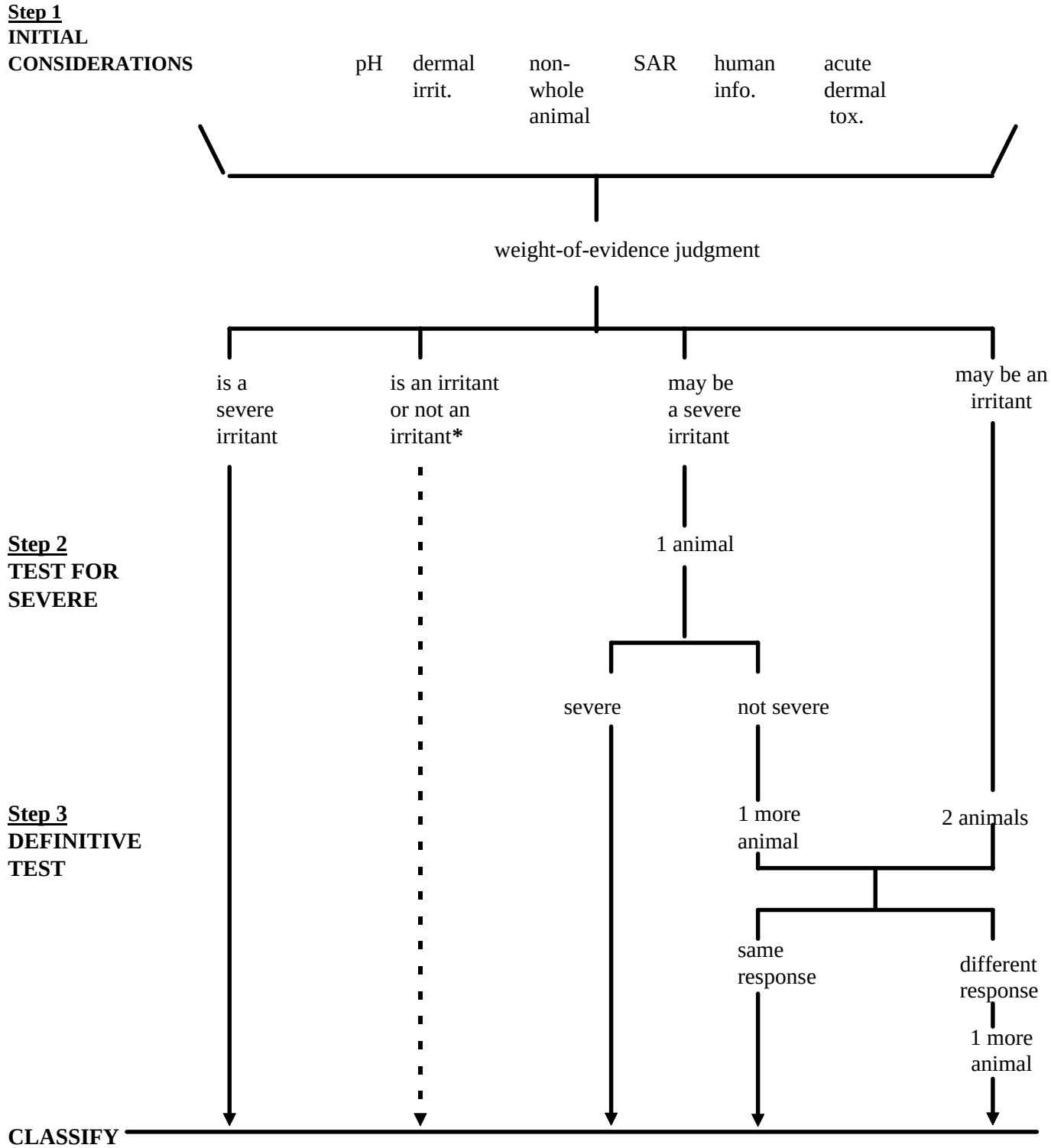
APPENDIX I
TIER SCHEME FOR EYE IRRITATION TESTING



***** Note: Under certain circumstances the evaluation of SAR, human experience and non-whole animal test information may allow one to make safety judgments concerning irritating or non-irritating responses (e.g., minor changes in the formulation of mixtures) that will not necessitate testing in animals.

APPENDIX II

Eye Irritancy Testing Strategy for New Chemicals within the Notification Procedure of the European Community

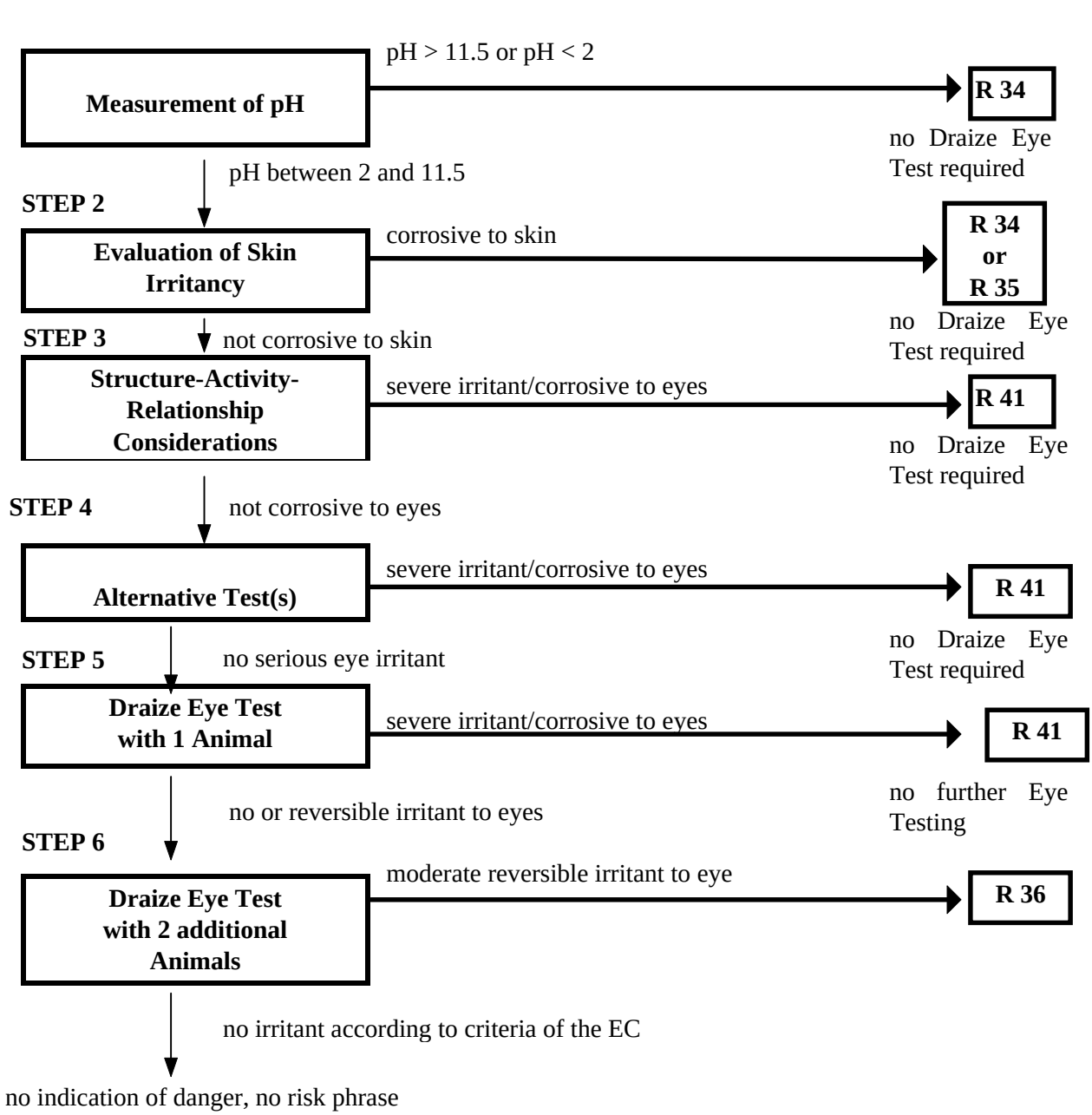


Table: Risk phrases for dangerous substances and preparations in the European Union

R34 Causes burns
full skin tissue destruction as a result of up to four hours exposure, or if this result can be predicted

R35 Causes severe burns
full skin tissue destruction as a result of a three minutes exposure, or if this result can be predicted

R36 Irritation to eyes
defined reversible changes of cornea, iris or conjunctiva

R38 Irritation to skin
defined reversible inflammation of the skin as a result of up to four hours of exposure

R 41 Risk of serious damage to eyes
defined severe reversible changes or irreversible changes of cornea, iris or conjunctiva