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

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No. 16

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

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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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 8).

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 Skin Irritation/Corrosion in OECD Member Countries has been prepared by a Joint United States and German Working Group as part of the work being carried out in the OECD's Programme on Harmonization of Classification and Labelling Systems.

This document has been produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

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GLOSSARY OF ACRONYMS

CPSC	Consumer Product Safety Commission
DOT	Department of Transportation
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act for US CPSC
IPCS	International Program on Chemical Safety
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
UN transport	United Nations Committee of Experts on the Transport of Dangerous Goods
US	United States

EVALUATION AND CLASSIFICATION SYSTEMS REVIEWED

Canada pesticides
Canada workplace
EU
Japan
Switzerland
Transport Canada
UN transport
US CPSC regulation
US CPSC policy which supersedes regulation
US DOT Norway US EPA pesticides (active ingredients)
US FDA policy for compliance monitoring
US OSHA

EXECUTIVE SUMMARY

A comparison of existing dermal irritation/corrosion hazard classification procedures currently in use is laid out, and issues requiring resolution are discussed. 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 general, the Canadian workplace and US EPA pesticide combined classes are the most sensitive in identifying chemicals as irritants. Canadian pesticide severe category, US EPA pesticides toxicity category II, and FHSA methods are the least sensitive. Intermediate are the Canadian pesticides combined categories and the EU 3-animal and 6-animal classification systems. In developing potential harmonized positions for dermal irritation/corrosion testing, two objectives have been kept in mind: to define criteria for both corrosion and 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 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; and at least 2 of 3 tested animals must be positive for the test to be positive. The proportion of test substances expected to be positive are investigated for three possible harmonized systems differing in the cutpoints for a positive mean score. The proportion of irritants would increase in comparison to the 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

The OECD in cooperation with the Coordinating Group on the Harmonization of Chemical Classification Systems has acted as a focal point for the harmonization of health and environmental hazard classification. At the first meeting of the Advisory Group on the Harmonization of Classification and Labelling on 27-28 February 1995 it was agreed that the United States would take the lead in assessing the current status of dermal irritation and corrosion. The present draft report develops these objectives: a presentation of the ways authorities evaluate test data and classify materials. A case study is included to illustrate how different authorities use data to make hazard classification decisions for dermal irritancy. In light of comments received on the May 1996 OECD Step 2 version of the harmonization proposal, a revised potential hazard classification system, including definitions and criteria, is proposed.

Sections of this report include initial considerations used to evaluate potential dermal effects or to determine the need for in vivo testing; the testing and evaluation of corrosion; and the testing and evaluation of irritation. A case study is included to illustrate how different authorities use data to make hazard classification decisions for dermal irritancy.

Several existing reviews were used as resources for developing this report (ECETOC, 1990, 1995; ICCA, 1994; Walker, 1990). Their ground breaking work is acknowledged.

INITIAL CONSIDERATONS

Various pieces of information are used prior to testing for dermal irritation and corrosion in rabbits; they are used to make classification decisions or to evaluate whether in vivo testing is needed (**Table 1**). For none of them is there unanimity among international authorities.

Table 1. Initial Considerations

Agency	SAR	pH	Acute dermal toxicity		Corrosive in vitro	Human experience
			Highly toxic	No effect at limit dose		
OECD, EU, Norway	+OECD; ±EU	≤2, ≥11.5, buffering	+	2000 mg/kg	+	+
UN transport	-	-	-	-	- UN; + Canadian transport, US DOT [a]	+
Canada workplace	+	≤2, ≥11.5, buffering	+	2000 mg/kg	-	+
Canada pesticides	± [b]	roughly ≤2, ≥11.5	+	-	-	+
US CPSC	-	-	-	-	-	+
US EPA pesticides & industrial chemicals	-	≤2, ≥11.5	+ [c]	-	-	-
US FDA policy	-	-	-	-	-	+
US OSHA	-	-	-	-	± [d]	+

Note: A (+) connotes use of a factor by an authority; (-) indicates silence on the factor.

a Uses results to define presence or absence of corrosive hazard: Corrositex for acids; acid derivatives (e.g., anhydrides, haloacids, salts); acyl halides; alkylamines & polyalkylamines; bases; chlorosilanes; metal & oxyhalides; and Skin^2 for acids; bases; quaternary ammoniums; surfactancts; silicates; hypochlorites.

b No SAR review of chemicals but of products/preparations with similar constituents; percentage noted of mineral & organic acids, alkaline materials, chlorine.

c Pesticides defines highly toxic as LD50 ≤200 mg/kg.

d In vitro studies alone generally do not form the basis for defining a hazard since they have a positive or negative result rather than a statistically significant finding.

Structure -Activity Relationships (SAR)

Canadian pesticides and workplace and OECD recognize the importance of SAR in deciding whether test materials are likely to have irritant potential (**Table 1**). EU points to organic hydroperoxides and organic peroxides as agents that are likely to be corrosive and irritating to the skin, respectively. Other authorities are silent on the subject

pH Extreme

Extremes of pH are identified by Canadian pesticides and workplace, EU, OECD, and US EPA pesticides and industrial chemicals as indicating potential severe dermal effects (**Table 1**). All of these but Canadian pesticides point out that a pH less than or equal to 2 or greater than or equal to 11.5 may be associated with serious dermal effects. EU and OECD emphasize the importance of knowing something about the buffering capacity of test materials with a pH extreme. Other authorities do not us pH extreme.

Acute Dermal Toxicity

Responses from acute dermal toxicity studies have been used to make determinations as to the need for dermal irritation and corrosion testing (**Table 1**). Canadian workplace, EU, OECD and US EPA pesticides state that highly toxic materials may not need testing; EPA defines highly toxic as an LD50 of 200 mg/kg or less. When no dermal irritation is noted at the limit dose in an acute dermal toxicity study (2000 mg/kg), Canadian workplace, EU and OECD state that dermal irritation and corrosion testing may not be needed.

In Vitro Alternatives

Although in vitro measures of dermal irritation and corrosion are recognized as initial considerations by EU, Norway and OECD, no such tests have been generally agreed upon at this time (**Table 1**). Canadian transport and US DOT have exemptions from in vivo testing for two in vitro alternatives (Corrositex and Skin^2), using test results on limited chemical classes for either defining corrosive hazard or absence of corrosivity. UN transport has not adopted these two alternatives, but allows competent authorities, like US DOT, to make their own determinations.

Human Experience

The majority of authorities use human information in making decisions about dermal reactions (**Table 1**). Canadian pesticides and workplace, EU, Norway, UN transport, US CPSC, US FDA, and US OSHA use responses in humans to make appropriate classification/regulatory decisions. No criteria are given for accepting human information. The EU allows for the recognition of potential effects in humans from materials with defatting properties that may lead to delayed reactions on the skin.

STATUS OF CORROSION

Definitions

There is a lack of agreement among authorities as to the definition of corrosion (**Table 2**). The various descriptions of corrosion skirt around the same findings, although some are more precise than others. Inclusive pathological descriptions have not been used. Generally corrosion is considered to be destruction of tissue through the epidermis down to some part of the dermis.

Table 2. Corrosion Definitions

Authority	Definition
Canada pesticides	Not specified; evaluations generally consistent with other authorities
Canada workplace	Like OECD/US EPA, or produces visual necrosis of human skin, or like UN transport
EU, UN transport	Produces full thickness destruction of skin tissue
Norway [a]	Permanent injury to tissue in intact skin
OECD/USEPA pesticides	Production of irreversible tissue damage in the skin
US CPSC, US FDA, US OSHA	Production of visible destruction or irreversible alterations in tissue at the site of contact

a: Plans to adopt EU definition

Use of Data for Classification

The evaluation and classification of corrosion is also not agreed upon (**Table 3**). Only the EU and Norway lay out specific criteria. They state that if at least one test animal manifests a corrosive action following exposures of up to 3 minutes or up to 4 hours, then the test material will be judged to cause severe burns (designated as R35) or causes burns (designated as R34), respectively. UN transport lays out specific exposure and observation/grading times for the development of corrosive reactions (for three packing groups), and US CPSC, US FDA policy, and US EPA pesticides state exposure times, but none of them give the number of animals that must show corrosive effects before an agent is classified as corrosive.

Table 3. Corrosion Evaluation and Classification

Agency	Classification	Criterion	
		Number of animals/Other	Exposure/ (Observation) time
Canada pesticides	corrosive	not stated	not stated
Canada workplace	corrosion	not stated but corrosive in OECD test, or like UN transport	not stated, or like UN
EU, Norway	corrosion-R 35-causes severe burns corrosion-R 34-causes burns	$\geq$ 1 animal $\geq$ 1 animal	$\leq$ 3 min $\leq$ 4 hr
UN transport	corrosive-packing group I corrosive-packing group II corrosive-packing group III	not stated	$\leq$ 3 min ($\leq$60 min) > 3 min - $\leq$1 hr ($\leq$14 days > 1 - $\leq$4 hr ($\leq$14 days)
US CPSC, US FDA policy	corrosive	not stated	4 hr
US DOT, US OSHA		like UN transport; for DOT, also Corrositex or Skin[2] (see Table 1)	
US EPA pesticides	corrosive-toxicity category I	not stated	4 hr

STATUS OF IRRITATION

Observation Times

Authorities vary as to when animals are observed and scored for dermal lesions (**Table 4**) and whether animals are followed to evaluate the reversibility of lesions. Most authorities gradelesions at (or around) 24, 48 and 72 hr after patch removal; fewer of them grade lesions within 1 hr of patch removal. None use times beyond 72 hr.

EU and US EPA pesticides recognize the importance of reversibility of lesions over time up to 14 days. Norway and OECD also call for the evaluation of reversibility of lesions, but a time limit is not given. All other authorities are silent on the use of reversibility of lesions.

Table 4. Observation and Grading Times

Authority	Hours after patch removal			
Canada workplace	1	24	48	72
Canada pesticides [a]		24		72
EU, Norway	1--observe, but do not grade	24	48	72
US CPSC		20		68
US OSHA	0		48	
US FDA policy	0.5	20	44	68
US EPA pesticides	1	24	48	72

a Classification can be increased in severity if it is known from acute dermal testing that lesions persist over time, e.g., at 14 d of observation.

Grading of Dermal Responses

All authorities use the same Draize et al. (1944) grading scale for dermal lesions given in (**Table 5**).

Table 5. Grading Effects on the Skin

Erythema and eschar formation	**Grade**
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema formation	**Grade**
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4

Evaluation

Authorities vary as to (a) the existence of criteria for evaluating irritation; (b) whether mean scores are computed for one time period or across all grading times; (c) whether endpoint grades are used alone (edema or erythema/eschar) or grades are pooled (edema plus erythema/eschar). For each of these, consult **Table 6**.

Criteria for evaluation of irritation are not given by Japan, Switzerland and US EPA industrial chemicals. In Switzerland, classification for acute oral toxicity is modified based upon information on dermal irritation and corrosion; it intends to adopt all EU hazard classification criteria in the future. Canadian workplace and pesticides, EU, Norway and US agencies (CPSC, EPA pesticides, FDA, OSHA) all have evaluation criteria.

Scoring varies from using a single observation time to averaging scores over time. Canadian workplace calculates averages at each of 4 observation times. All other authorities average across observation times.

Pooling scores across animals and scoring each animal separately are found. EU and Norway determine mean scores for each animal separately for 3-animal tests. However in the case of 6-animal tests for EU, Canadian pesticides and workplace, and for US agencies (CPSC, EPA pesticides, FDA, OSHA), scores are pooled across animals.

Using endpoints separately or pooled is noted. Canadian workplace, EU and Norway calculate mean scores for erythema/eschar and for edema separately. Canadian pesticides and US agencies (CPSC, EPA pesticides, FDA, OSHA) pool grades across both endpoints. evaluated and classed (**Table 6**). Canadian workplace calculates a mean score by averaging responses across 3 animals for edema grades and for erythema/eschar grades, separately. Averaging is done for each of four scoring times (1, 24, 48 and 72 hours after patch removal). A test is positive for irritation when a mean score of 2 or more is computed for at least one scoring time.

EU and Norway (for a 3-animal test) calculate mean score across 3 scoring times (24, 48 and 72 hr after patch removal) for each animal for edema grades and for erythema/eschar grades, separately. An animal is positive when the mean score is 2 or greater. The test is positive for irritation when at least 2 animals are positive for the same endpoint (erythema/eschar or edema). For a 6-animal test a mean score is calculated across 3 scoring times (as above) and across all 6 animals for edema grades and for erythema/eschar grades, separately,. A mean score of 2 or more identifies an irritant.

Table 6. Irritation Evaluation and Classification: Criteria for Positive Test

Agency	Classification	Criteria	Mean score components [w]
		Mean score/other	
Canada pesticides	severe irritant moderate irritant mild irritant	>5.0 3.1-5.0 1.6-3.0	(sum 2e x 6a x 2t x 1g)/12 [x]
Canada workplace	irritant	≥2.0 at any 1 of 4 scoring times	(each e x 3a x 1t x 1g)/3
EU, Norway [y]	irritant	≥2.0 for 6 animal test, ≥2.0 in ≥2 animals for 3 animal test, or inflammation at end of test (14 d) in ≥2 animals [z]	(each e x 6a x 3t x 1g)/18 (each e x 1a x 3t x 1g)/3
Japan, Switzerland [v]		no quantitative criteria	
US CPSC regulation/ US OSHA	irritant	≥5.0	(sum 2e x 6a x 2t x 2g)/24
US CPSC policy/US FDA policy	irritant	≥5.0	(sum 2e x 6a x 4t x 2g)/48
US EPA pesticides	toxicity category II toxicity category III toxicity category IV	>5.0 2.0-5.0 <2.0	(sum 2e x 6a x 4t x 1g)/24

a Animals (see footnote w).
e Endpoints: erythema/eschar, edema (see footnote w).
g Groups: intact skin (1), or intact + abraded skin (2) (see footnote w).
t Scoring times (see footnote w).
v Switzerland intends to adopt EU criteria in the future.
w To calculate mean scores and evaluate results using Canada workplace as an example: for either endpoint (erythema/eschar or edema), sum the grades from 3 animals at a given scoring time (1, 24, 48, 72 hr); divide the sum by 3, the number of observation units. Repeat the process for each of the other three scoring times. If any of the four mean scores is 2 or more, the test is positive. Repeat process for the other endpoint.
x Generally use 24 and 72 hr scores (but may use 4 scoring times as in EPA); consideration also given to protocol deviations &/or scoring modifications (i.e., <6 animals, >2 time points), & calculation adjustments made accordingly.
y Animals must demonstrate same lesions; EU has 6-animal evaluation guidance but no testing guideline.
z Particular effects should be evaluated, e.g., alopecia, discoloration, fissures, hyperplasia, scabs and scaling.

Given the above differences, there are several ways in which irritation test results are. An irritant can also be established for either the 3-animal or the 6-animal test by the finding of inflammation of the skin at the end of 14 days of observation in 2 or more animals. Certain effects are considered, e.g., alopecia, discoloration, fissures, hyperplasia, scabs and scaling.

Canadian pesticides, US CPSC, US EPA pesticides, US FDA & US OSHA calculate mean scores for combined grades for edema and for erythema/eschar, across 6 animals and across each of the scoring time periods. (See section 4.1 above for the scoring times used).

Case Study

Tissue grades and findings are recorded for a 6-animal test of dermal irritation for a hypothetical test material in **Table 7.** Grades for edema and erythema/eschar are presented for 1, 24, 48 and 72 hours after patch removal from both intact and abraded skin areas. Skin lesions noted at the end of the study at 14 days are presented. Mean score calculations are computed, and classification decisions are shown for several different international authorities using the case study data, as appropriate.

The test material was defined as being an irritant according to the EU 6-animal and 3-animal evaluation schemes and Canadian workplace. For authorities with multiple irritant classes, intermediate but not the most risk averse designations of toxicity were noted: Canadian pesticides (moderate irritant), and US EPA pesticides (toxicity category III). Evaluation by the US CPSC, US FDA policy and US OSHA systems resulted in the material being classed as non-irritant.

ISSUES FOR RESOLUTION

Initial Considerations

What factors should be evaluated prior to in vivo testing for dermal corrosion and irritation?

Authorities vary in the factors that are considered before in vivo testing. All the various initial considerations currently being used by different authorities all seem to have a rational basis. They include: historical human experience, SAR, pH extremes, acute dermal toxicity findings, results of in vitro test results. The more information that is reviewed, the more likely preliminary hazard decisions can be made that would obviate the need for any in vivo dermal testing, an obvious benefit.

Human experience with irritating and corrosive materials is not extensive, but it can be very illuminating when it exists; after all, the responses are in the species of concern. SAR can be helpful in identifying certain potentially corrosive and irritating substances, like organic peroxides and other groupings. Extremes of pH (≤ 2, ≥ 11.5) are good indicators of corrosivity, especially when buffering capacity is considered. However, without consideration of acid and alkaline reserve, deviations from expectation may be noted.

When acute dermal toxicity has been done prior to irritation testing, it makes sense that an agent need not be tested when there is no dermal reaction from testing at the limit dose of 2000 mg /kg or when an agent is highly toxic via the dermal route, e.g., LD50 $\leq$ 200 mg/kg. Use of this information requires that careful records are kept when performing these acute toxicity tests, so that the findings can be applied to the evaluation of dermal corrosion and irritation.

In vitro test measures have great promise for detecting potentially corrosive or irritating materials, but no methods have yet been found internationally acceptable. Unfortunately, validation of these tests has been long in the coming. It may also be possible in the future to find a battery of in vitro methods that may absolve an agent as being corrosive or irritating. Much more work is needed.

Can tier approaches be utilized to organize initial considerations?

Germany has proposed and the OECD workshop on alternatives in Solna, Sweden has recommended that a specified tiered approach to evaluating initial information be adopted

Table 7. Case Study: Dermal Irritation Data

	Intact Skin									Abraded Skin								
	Erythema/eschar for times				Edema for times				Other lesions	Erythema/eschar for times				Edema for times			
Animal	1h	1d	2d	3d	1h	1d	2d	3d	14d [a]	1h	1d	2d	3d	1h	1d	2d	3d
1	3	2	2	2	3	3	3	3	+	3	3	3	3	3	4	4	4
2	1	1	1	1	2	2	3	3	-	2	3	3	2	2	2	2	3
3	2	1	1	1	3	3	3	2	-	1	2	2	3	3	2	2	2
4	2	2	3	3	4	4	2	2	-	2	2	3	3	4	4	4	4
5	1	2	3	2	2	3	3	4	+	2	2	2	3	3	3	3	2
6	3	2	2	1	2	2	3	2	-	3	2	2	1	2	3	3	4
Sums																	
First 3 animals	6	4	4	4	8	8	9	8									
All 6 animals	12	10	12	10	16	17	16	16		13	14	14	14	17	18	18	19
1d + 2d + 3 d	32				49					42				55			
1h + 1d + 2d + 3d	44				65					55				72			

a At end of observation at 14 d, scabs and skin discoloration were noted in (+) animals

Table 7. (Continued) Case Study: Evaluation/Classification

Authority	Grade sum	Animal x time x group scoring units	Mean score	Animal response	Class
EU, Norway					
6-animal test					
a. erythema/eschar	32	÷ 18	= 1.8		non-irritant
b. edema	49	÷ 18	= 2.7		irritant
c. end of observation	animals 1 & 5 had lesions				irritant
3-animal test					
a. erythema/eschar	Use first 3 animals	÷ 3	= 2.0	+	non-irritant
	animal 1 6	÷ 3	= 1.0	-	
	animal 2 3	÷ 3	= 1.0	-	
	animal 3 3				
b. edema		÷ 3	= 3.0	+	irritant
	animal 1 9	÷ 3	= 2.7	+	
	animal 2 8	÷ 3	= 2.2	+	
	animal 3 7				
c. end of observation	animal 1 had lesions				non-irritant
Canada pesticides	10 + 10 + 17 + 16 = 53	÷ 12	= 4.4		moderate irritant
Canada workplace					
3-animal test	Use first 3 animals				
a. erythema/eschar	6, 4, 4, or 4	÷ 3	= ≥2.0 for 1 of 4 times		non-irritant
b. edema	8, 8, 9, or 8	÷ 3	= ≥2.0 for 4 of 4 times		irritant
US CPSC regulation/ US OSHA	Use 1 d & 3d 10 +10 + 17 + 16 + 14 +14 + 18 + 19 = 118	÷ 24	= 4.9		non-irritant
US CPSC policy/ US FDA policy	Use all 4 scoring times 44 + 65 + 55+ 72 = 236	÷ 48	= 4.9		non-irritant
US EPA pesticides	44 + 65 = 109	÷ 24	= 4.5		irritant, toxicity category III

(Schlede & Gerner, 1995; OECD, 1996).

Such an approach may be useful in evaluating new chemicals within a given regulatory framework, like the EU industrial chemicals program, however, it may not be applicable under all circumstances. Many authorities cannot prescribe the types and order of testing and evaluation. In addition, for existing chemicals, some information is generally available, while others are missing. Nevertheless, a tiered scheme may indirectly help to organize information so that it can be appropriately analyzed, and it may be directly applicable under other regulatory circumstances. This should be done with the understanding that data may not be available for all of the tiers or existing information may not be applicable in all situations.

Corrosion

Authorities vary on the descriptive definitions of corrosion. They vary in their use of reversibility information in making decisions about corrosivity. Differences exist as to the number of animals used for testing; the number of animals needed to define a positive test; number of sites of test substance application per animal; exposure and observation times; the number and names of corrosion categories. Each will be discussed.

How should corrosion be defined?

Current use of descriptors like full or whole thickness destruction may be somewhat of an overstatement, as tissue destruction need not include all of the dermis, only part of it. Likewise, visible necrosis or destruction is not very specific, as is irreversible or permanent injury. Attempts should be made to be more specific and use pathological terms where appropriate.

What are the pathological characteristics of corrosion and when are they manifest?

Certain findings in a study indicate a corrosive reaction. Authorities have not described the various manifestations. In some cases corrosive manifestations are noted soon after application to the skin, however, ofttimes it takes a period of days for the process to reach maximum intensity. Corrosion involves destruction of the epidermis and down into the dermis. When there is frank bleeding or bloody scabs (eschar) it is obvious that the epidermal basement membrane has been breached and the process has entered the dermis. Over time there is often blanching of the skin due to the loss of pigment cells.. Since hair follicles are embedded in the dermis, areas of alopecia also herald corrosivity. Histopathology can give a definitive diagnosis and has much to recommend it. Note that vesicles are an indication of irritation, not corrosion, as they represent disturbances at the epidermal-dermal interface.

Irritation

What are the pathological characteristics of irritation, and when are they manifest?

Authorities recognize that erythema/eschar and edema are manifestations of dermal irritation, but they fail to provide further guidance. Irritation is initially manifest by redness (erythema), vesicles, serous exudates, serous scabs (eschar) and various degrees of swelling (edema). Over time, other reactions may be manifest, like small areas of alopecia, hyperkeratosis, hyperplasia and scaling. Histopathology is useful in discerning among responses and should be encouraged.

In most cases inflammation is well developed within the first 72 hr of observation. This has led authorities to commonly use grades at 24, 48 and 72 hr to evaluate irritancy potential. In some cases, like with defatting agents and certain petroleum distillate containing products, inflammatory responses may be delayed to later time periods. Certainly these are manifestations of irritation.

Are animal responses homogeneous?

Like with corrosion, irritation responses are not necessarily homogeneous across test animals. Some animals may show pronounced irritation while others are largely unaffected. How humans may respond is largely unknown, although generally it is thought that animals are more sensitive than humans.

Should endpoints be scored separately?

Erythema/eschar and edema are graded consistently by all authorities using the Draize scale. Some authorities grade the two endpoints separately, while others pool grades across endpoints. Some test materials essentially produce only one type of response. Such cases would be under reported as irritants if evaluations were made by pooling grades across both endpoints when, in fact, they are irritating..

What are the relative sensitivities of existing hazard classification systems?

Most authorities have a single class for dermal irritation. The exceptions are the pesticide programs of Canada and the US, where several classes of varying severity are used to help differentiate the types of protective clothing that would be worn by pesticide applicators. These are important considerations to ensure the safety of workers.

There are many ways authorities use test data to make classification decisions (**Tables 6** and **7**). To help compare the relative sensitivity of the various classification systems currently in use in OECD countries, data have been obtained from a number of tested materials and used to compare the proportion of irritants across systems (**Table 8**). Information includes 21 tests of 20 household products (6-animal tests; intact and abraded skin) from the US CPSC, 21 tests of 19 industrial chemicals from the ECETOC data base (3 or 4-animal tests; intact skin only) (ECETOC, 1995), and 12 surfactants (3-animal tests; intact skin only) from a classified source from the files of the US FDA.

Classification using the US CPSC/US FDA method (designated FHSA in the figure below) was possible only for the 21 chemicals from the US CPSC files, because they were the only tests done with both intact and abraded skin. FHSA determinations were also made using intact skin results whether data were from 6-animal or 3-animal tests. For other classification systems using the US CPSC data set, grades were only used from intact skin. For determinations using 6 animal test data under the EU system, a test was declared positive when at least 4 animals were positive; at least 2 positive animals were required for a positive test for 3-animal tests. Evaluations could be conducted on 18 of 21 ECETOC tests using the EU system.

Table 8. Proportion of Irritants Under Existing Systems

Database	EU 3	EU 6	EPA II	EPA III	FHSA	FHSA Intact	Can Pest S	Can Pest M	Can Work
US CPSC (n = 21)	.62	.67	.24	.71	.43	.29	.29	.43	.95
ECETOC (n = 21)	.61 (n=18)	.52	.10	.52	N/A	.10	.14	.38	.62
US FDA (n = 12)	.50	N/A	.33	.33	N/A	.33	.33	.17	.67
Total	**.59**	**.60**	**.20**	**.56**	**.43**	**.22**	**.24**	**.35**	**.76**

Legend :

Can Pest S	Canadian pesticides severe category
Can Pest M	Canadian pesticides moderate category
Can Work	Canadian workplace
EPA II	US EPA pesticides toxicity category II
EPA III	US EPA pesticides toxicity category III
EU 3	EU classification for 3-animal test
EU 6	EU classification for 6-animal test
FHSA	US CPSC/US FDA using both intact and abraded skin grades and FDA grading times
FHSA Intact	As above, using only intact skin grades
N/A	Not applicable

The proportion of irritant chemicals for a given classification system varies among the data bases. In each case, Canadian workplace and US EPA pesticides combined toxicity categories II and III are the most sensitive in identifying chemicals as irritants. Canadian pesticides severe category, US EPA pesticides toxicity category II, and FHSA methods are the least sensitive. Intermediate between these two groupings are the Canadian pesticides combined severe and moderate categories and the EU 3-animal and 6-animal classification systems, which are comparable to each other.

As a means of possibly developing a potential harmonized position, three characteristics are kept in mind: (a) to use an existing scoring system; (b) to develop a harmonized position that is public health protective but does not require significant modification in existing chemical classifications; and (c) to make available hazard subclasses for those authorities that wish to use them. The EU 3-animal scoring method is used as the model classification system. The consequences of modifiying the cutpoints for a positive test and for subclasses are presented in **Table 9**. The same data that are used in **Table 8** are employed for three other optional classifications: in option A, a test material is positive if the mean score from three observation times in at least 2 of 3 animals is $\geq$ 1.3; in options B and C, a test is positive if the mean score is $\geq$ 1.5. For those authorities that want to have subclasses, for option A the cutoff groupings are

≥ 1.3 - < 2.3 for subclass A1 and ≥ 2.3 - 4.0 for subclass A2. For option B the cutoff groupings are ≥ 1.5 - < 2.5 for subclass B1 and ≥ 2.5 - ≤ 4.0 for subclass B2. Finally, for option C, the cutoffs are ≥ 1.5 - < 2.3 for subclass C1 and ≥ 2.3 - ≤ 4.0 for subclass C2. The number of test substances used for scoring varies slightly in the table because of the cutpoints used.

The total proportion of irritants for option A is 0.79, for options B and C is 0.68, and for the existing EU 3-animal test (criterion mean score ≥ 2.0) is 0.59. The proposed options would increase in the proportion of irritants for the EU and combined severe and moderate Canadian pesticide systems and especially for the FHSA method. The proposed options are more in keeping with the existing Canadian workplace and combined category II and III EPA pesticides systems. The subclasses could be used by Canadian and US pesticides authorities; overall, the subclasses for option C have about equal numbers of positives. The proposed options may serve as a basis for establishing a harmonized classification system.

Table 9. Proportion (Number) of Irritants as a Function of Mean Score Cutpoints

Database	Option A			Option B		
	Subclass A1	**Subclass A2**		**Subclass B1**	**Subclass B2**	
	≥ 1.3 - < 2.3	**≥ 2.3 - ≤ 4.0**	**Combined**	**≥ 1.5 - < 2.5**	**≥ 2.5 - ≤ 4.0**	**Combined**
CPSC (n = 21)	.38 (n = 8)	.43 (n = 9)	.81 (n = 17)	.33 (n = 7)	.38 (n = 8)	.71 (n = 15)
ECETOC (n = 19) [a]	.63 (n = 12)	.21 (n = 4)	.84 (n = 16)	.53 (n=9)	.18 (n = 3)	.71 (n = 12)
FDA (n = 12)	.33 (n = 4)	.33 (n = 4)	.67 (n = 8)	.25 (n = 3)	.33 (n = 4)	.58 (n = 7)
Total (n = 52)	**.46 (n = 24)**	**.33 (n = 17)**	**.79 (n = 41)**	**.38 (n = 19)**	**.30 (n = 15)**	**.68 (n = 34)**

Database	Option C		
	Subclass C1	**Subclass C2**	
	1.5 - < 2.3	**2.3 - ≤ 4.0**	**Combined**
CPSC (n=21)	.28% (n=6)	.43 (n=9)	.71 (n=15)
ECETOC (n=17)	.47 (n=8)	.24 (n=4)	.71 (n=12)
FDA (n=12)	.25 (n=3)	.33 (n=4)	.58 (n=7)
Total (n=50)	**.34 (n=17)**	**.34 (n=17)**	**.68 (n=34)**

a: number of chemicals for option B is n = 17

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