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EXAMINATION OF A PROPOSED SKIN NOTATION STRATEGY

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European Centre for Ecotoxicology and Toxicology of Chemicals

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SUMMARY

A Skin Notation is an indication added to an Occupational Exposure Limit (OEL) for those substances for which skin absorption, in addition to inhalation exposure, may lead to adverse health effects. An ECETOC Task Force proposed a strategy for assigning a Skin Notation based on principles used by the Dutch Expert Committee on Occupational Standards (DECOS). This was published in ECETOC Document No. 31 (revised).

This further document describes the application of the proposed strategy to 36 substances and compares the results with the designations given in five reference countries, viz. UK, Germany, Sweden, the Netherlands and the USA.

The ECETOC proposed scheme was used to arrive at the conclusions. Relevant data including the EC classification of a substance, information from case reports on human exposure, and quantitative human and animal data from both *in vivo* and *in vitro* studies, were taken into account. When quantitative data on skin absorption were available, the partial contribution by skin absorption to the total exposure based on systemic effects was calculated. When quantitative data were not available the importance of skin absorption was deduced from a comparison of the dermal LD_{50} with the intravenous LD_{50}, the intraperitoneal LD_{50} or the acute LC_{50} by inhalation. The TF accepted as legitimate the exemption of those substances with a low toxicity profile as specified in the report. The assessments for the individual substances are described briefly in Appendix C to the report.

The sensitivity of the ECETOC scheme when compared with the unanimous and majority (4/5) positive decisions by the reference countries was 83% and 88% respectively. The respective specificities were 100% and 69%.

Due to the lack of consistency within the designations given in the reference countries no correlation could be established for 7 of 36 substances. The scheme did not allow a decision for another 6 substances on the basis either of inadequate data or inappropriateness for gases.

The TF concluded that the strategy proposed by ECETOC offered a transparent scheme for the future assessment of the need to apply a Skin Notation to an individual substance and recommends its general use.

1. INTRODUCTION

For certain substances, skin absorption may be an important source of occupational exposure. For this reason lists of occupational exposure limits (OELs) often provide a Skin Notation which indicates that adverse effects may arise from skin absorption as well as inhalation exposure. Up till now there has been little transparency in the criteria applied by the various expert bodies when deciding on the need for a Skin Notation.

ECETOC Document No. 31 (Revised, 1993) entitled Strategy for Assigning a "Skin Notation" reviewed the factors underlying the criteria and made proposals for a scheme to assist in the achievement of a transparent approach (Appendix A). It was recommended however that the proposed approach be reviewed in the light of experience in use, any formal validation undertaken and any scientific or technical progress.

Subsequently an ECETOC Task Force was established with the following Terms of Reference:

- Determine a set of suitable test chemicals with an OEL and an adequate data base and independently evaluate the basis for the existing Skin Notation;

- assemble the necessary data for the application of the ECETOC proposed strategy and use them to determine the resulting Skin Notation;

- discuss the concordance and differences between the conclusions derived from the ECETOC proposed strategy and the existing Skin Notation status and make recommendations concerning the ECETOC proposals.

The objectives of the TF were thus to validate the ECETOC proposed decision scheme, to provide worked examples and to give guidance for those developing guidelines for OELs, particularly in relation to the assignment of a Skin Notation in combination with an OEL. In applying the scheme the TF had the opportunity to revisit the principles involved.

This Document reports on the application of the scheme to 36 substances for some of which there was a consensus in the reference countries that a Skin Notation was either required or not required and others for which were was no consensus.

The TF evaluated the proposed strategy employing the data selected. The quality of the available data base was not reviewed in depth by the TF, nor were explanations sought for the different conclusions reached by the reference countries.

2. METHODOLOGY

The decision tree, as originally presented in Document 31 (Revised) is included, for ease of reference as a "flip-out" at the back of the report. For the purposes of this examination of the proposed strategy by the current TF, it has been made more transparent by numbering and providing written guidance to the various steps involved; details are presented below.

ECETOC Decision Scheme Leading to a Skin Notation

1. Does or should the substance carry a health classification according to EC Directive 67/548/EC ?

   - **No: no Skin Notation**
   - Yes: go to step 2

2. Does circumstantial and/or other human evidence indicate skin penetration ? (Appendix A, Section 2.4 (a))

   - No: go to step 3
   - **Yes: Skin Notation**

3. Are skin penetration data available ? (Appendix A, Section 2.4 (c))

   - No: go to step 6
   - Yes: calculate penetration rate and go to point 4

4. Is the (S)OEL based on systemic toxicity ? (Appendix A, Section 2.5)

   - No: determine a (S)OEL using the systemic data available and go to step 5
   - Yes: go directly to step 5

5. Compare penetration rate with the Critical Absorption Value (CAV) (Appendix A, Section 2.5)

   Is the CAV $\geq$ 0.25 (S)OEL ?

   - **No: no Skin Notation**
   - **Yes: Skin Notation**

6. Is Skin Notation considered important according to criteria ? (Appendix A, Section 2.4 c,d and 2.5) ?

   - **No: no Skin Notation**
   - Yes: go to step 7

7. Can the substance be excluded on the basis of low toxicity ? (Appendix A, Section 2.4 (c2))

   - **No: Skin Notation**
   - Yes: go to step 8

8. Is or should the substance be classified for serious long-term or specific health effects?

   - **No: no Skin Notation**
   - **Yes: Skin Notation**

In the data sheet compiled for each substance and presented in Appendix C, the information and assessments are presented in the order of the various steps of the decision scheme. At the end of each evaluation the conclusion reached by the TF was compared with the conclusions reached in the 5 reference countries, namely:

- USA. American Conference of Governmental Industrial Hygienists (ACGIH);
- Germany. German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (D);
- The Netherlands. Dutch Expert Committee on Occupational Standards (DECOS) (NL);
- Sweden. Swedish National Board of Occupational Safety and Health (S);
- UK. Working Group on the Assessment of Toxic Chemicals (WATCH) (UK).

Information on these conclusions was obtained from the International Labour Office data base (1992; ExpoLim. FM, Assit, Switzerland).

Thirty six substances were selected on the basis of availability of reviews as indicated in ECETOC Technical Report 30(5), 1994 and on the availability of OELs in 5 countries. Using the ECETOC decision scheme, these substances were assessed individually by the Task Force (TF). The method of working was for each individual TF member to collect data and generate a working sheet for each specific

substance, containing the information that was applied in following the decision path. These working sheets, sequentially-numbered according to CAS number, were reviewed by the TF leading to the final assessments as presented in Appendix C.

The steps in the decision scheme took into account the following:

- Important characteristics of the substance (physical state, boiling point and vapour pressure);
- relevant data on the substance, including EC classification according to the “Classification and Labelling of Dangerous Substances" Directive (67/548/EEC);
- information from case reports on human exposure;
- quantitative data from both *in vivo* and *in vitro* studies.

When quantitative data on skin absorption were available, the partial contribution by skin absorption to the total OEL, when based on systemic effect, was calculated. Preference was given to *in vivo* data. When quantitative data were not available, the importance of skin absorption was deduced from a comparison of the dermal LD50 with the intravenous LD50, the intraperitoneal LD50 or the acute LD50 by inhalation. To enable extrapolation from different types of quantitative data, standardised units were used for body weight, body part surfaces and inhalation rates for various animal species and man (Appendix B). For the mouse and the rat, difference in strain or the age of the animal at the moment of test resulted in different body weights. Some of these values are taken from the literature as indicated; others were agreed by the TF.

The general information on skin absorption and Skin Notation was reviewed as it appeared in the different guidance documents on exposure limits for the workplace in the 5 reference countries (Appendix D).

3. RESULTS

An overview of the results obtained using the ECETOC scheme is given in Tables 1a-4b.

All tables indicate:

- the number allocated to the substance and used in Appendix C;
- the CAS-number;
- the name of the substance;
- the steps of the decision scheme (Section 2. Methodology) followed to reach the conclusion as to whether or not a Skin Notation was appropriate.

Brief comments are included to indicate the basis for the TF decision (see Appendix C for further details).

1a) Unanimous agreement in reference countries on need for a Skin Notation

Table 1a: Decision steps followed by TF

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
1	62-53-3	Aniline	Y	Y	Y[b]	Y[b]	Y[b]				Y
7	75-15-0	Carbon disulphide	Y	Y	Y[b]	Y[b]	Y[b]				Y
13	98-01-1	Furfural	Y	N	Y	Y	Y				Y
24	108-11-2	Isobutyl methylcarbinol	Y	N	N			Y	Y	N	N
27	111-40-0	Diethylene triamine[a]	Y	N	N			Y	N		Y
28	111-76-2	2-Butoxyethanol	Y	Y/N	Y	Y	Y				Y

Y = Yes
N = No

[a] Compound only listed by 4/5 countries
[b] These steps were confirmatory

Comment

The ECETOC decision scheme led to a recommendation for a Skin Notation for all but one substance, namely isobutyl methyl carbinol (24).

A comparison of the acute toxicity data for isobutyl methyl carbinol resulted in a ratio of <10 for $LD_{50\text{-inh}}$ / $LD_{50\text{-dermal}}$. The actual toxicity data indicated a low toxicity, making a Skin Notation irrelevant. Since there were no other reasons for concern, the conclusion from the ECETOC strategy that no Skin Notation was recommended seems reasonable. The recommendation for a Skin Notation by the reference countries might be based on the moderate skin irritancy of isobutyl methyl carbinol. Irritation in itself is not considered by ECETOC to justify a Skin Notation.

In four cases, but not including the exception, quantitative skin absorption data from volunteers were available.

For diethylene triamine (27), no data on quantitative dermal absorption or on relevant acute toxicity were available. Corrosivity, coupled with a very low $LC_{50,}$ caused concern that the dermal absorption might be significant. This led (via steps 6 and 7) to the decision that a Skin Notation was appropriate.

1b) Need for Skin Notation agreed in 4/5 countries

Table 1b: Decision steps followed by TF

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
10	77-78-1	Dimethyl sulphate	Y	N	N			Y	N		Y
34	591-78-6	Hexan-2-one	Y	N	Y	Y	Y				Y

Y = Yes
N = No

Comment

For the substances in Table 1b, the ECETOC decision scheme led to a recommendation for a Skin Notation; this was in agreement with the majority of the 5 reference countries.

For dimethyl sulphate (10) although there were no quantitative data on skin absorption or on relevant acute toxicity, delayed-type corrosivity coupled with a very low LC_{50} caused concern that dermal absorption might be significant. This led (via steps 6 and 7) to the decision that a Skin Notation was appropriate.

2a) Unanimous agreement in reference countries (5) that no Skin Notation was needed

Table 2a: Decision steps followed by TF

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
5	75-05-8	Acetonitrile	Y	N	N			Y/N			N
9	75-56-9	1,2-Epoxypropane	Y	N	N			N			N
11	78-83-1	Isobutanol	Y	N	N			Y	Y	N	N
21	107-21-1	Ethylene glycol	Y	N	N			Y	Y	N	N
26	110-54-3	n-Hexane	Y	N	Y	Y	N				N
32	141-43-5	Ethanolamine	Y	N	Y	Y	Y/N				N

Y = Yes
N = No

Comment

For the substances in Table 2a the ECETOC decision scheme led to the recommendation that a Skin Notation was not necessary; this is in complete agreement with the reference countries.

For n-hexane (26) and ethanolamine (32) the conclusion was based on quantitative skin absorption data. For n-hexane the quantitative data on dermal absorption in guinea pig (*in vitro*) were two orders of magnitude higher than *in vivo* data from rats. In either case, the Critical Absorption Value (CAV) was higher than any of these values, indicating that no Skin Notation was necessary. With ethanolamine, local biochemical reactions at the site of dermal absorption prevent any systemic activity of this substance, otherwise a Skin Notation would have been appropriate. This interpretation was considered to be in agreement with the general statement on industrial experience (Appendix A, Section 2.5).

For acetonitrile (5) there were no data on dermal absorption and the TF considered that the data on dermal toxicity were inconsistent and could lead to either a "yes" or a "no". In this case the absence of reported cases during considerable industrial experience ‘tipped the balance’ and no Skin Notation was recommended.

In the case of epoxypropane (9), an animal carcinogen, the decision scheme ended where the data indicated no significant skin absorption and therefore no significant risk of systemic carcinogenesis. As is the case with skin irritants, the possibility of local carcinogenic effects on the skin should be evident through the classification and labelling of the product.

For isobutanol (11) and ethylene glycol (21) no quantitative data on skin absorption were available. Comparison of dermal and other routes of exposure suggested that skin uptake could be significant. However a Skin Notation was not considered necessary, based on low toxicity and an absence of other reasons for concern.

2b) No need for Skin Notation agreed in 4/5 countries

Table 2b: Decision steps followed by TF

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
6	75-09-2	Dichloromethane	Y	N	Y	Y	Y				Y
18	106-87-6	1,2-Epoxy-4-epoxyethylcyclohexane	Y	N	N			Y	N		Y
20	107-06-2	1,2-Dichloroethane	Y	N	Y	Y	Y				Y
22	107-98-2	1-Methoxypropanol-2	N								N
23	108-10-1	Methyl isobutyl ketone	N								N
33	542-75-6	1,3-Dichloropropene	Y	N	N			Y	N		Y
36	34590-94-8	Dipropylene glycol methyl ether	N								N

Y = Yes
N = No

Comment

The ECETOC decision scheme led to the conclusion that no Skin Notation was necessary for 3/7 chemicals for which there was near agreement amongst the 5 reference countries that it was not necessary; for 4/7 substances it led to the opposite conclusion.

For dichloromethane (6), quantitative skin absorption data were available from volunteers. The decision scheme led to a Skin Notation recommendation.

The need for a Skin Notation for 1-methoxypropanol-2 (22) and dipropylene glycol methyl ether (36) was excluded on the basis of low toxicity.

No quantitative skin absorption data were found for 1,2-epoxy-4-epoxyethyl cyclohexane (18) or for 1,3-dichloropropene (33), yet acute toxicity data indicated that skin absorption was significant and a Skin Notation was appropriate.

In the case of 1,2-dichlorethane (20) the opposite conclusion would have been reached using the alternative decision path had skin absorption data not been available. This illustrates the importance of using quantitative skin penetration data.

3) No consensus between reference countries on need for a Skin Notation

Table 3: Decision steps followed by TF

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
2	68-11-1	Mercaptoacetic acid	Y	N	N			Y	N		Y
3	71-43-2	Benzene	Y	N	Y	Y	Y				Y
14	100-41-4	Ethyl benzene	Y	N	Y	Y	Y				Y
15	100-42-5	Styrene	Y	N	Y	Y	N				N
16	101-14-4	4,4'-Diamino-3,3'- dichlorodiphenylmethane	Y	N	Y	Y	Y				Y
17	101-77-9	4,4'-Methylenedianiline	Y	Y							Y
19	106-92-3	1-Allyl-2,3-epoxypropyl ether	Y	N	N			N			N
31	127-18-4	Tetrachloroethylene	Y	N	Y	Y	Y				Y
35	1330-20-7	Xylene (3 isomers)	Y	N	N			N			N

Y = Yes
N = No

Comment

For styrene (15) no Skin Notation was considered necessary, based on quantitative skin absorption data. The Critical Absorption Value (CAV) was higher than the measured absorption with an OEL of 50 ppm (the OEL adopted by most countries). However, should an OEL of 20 ppm be chosen, the CAV would be below the measured absorption value. In cases such as styrene a final check versus industrial experience may 'tip the balance'.

For 1-allyl-2,3-expoxypropyl ether (19) without quantitative data on dermal absorption, the comparison of the acute dermal toxicity with the toxicity by inhalation, indicated that the dermal absorption was not significant. The decision that no Skin Notation was necessary followed directly from this.

For six substances (2, 3, 14, 15, 16 and 31**)** with quantitative data on skin absorption, the assessment route led to a Skin Notation recommendation. For four of these (2, 3, 14 and 15) human volunteer data were available; for (16) and (31) *in vitro* human skin and *in vivo* rabbit data respectively were available, including measurement of the excreted amount.

Human experience with 4,4-methylenedianiline (17) indicated that a Skin Notation was necessary.

For xylenes (35) there were no quantitative data on skin absorption. Comparison of dermal and other routes of exposure suggest that skin uptake could be significant. However no Skin Notation was considered necessary based on low toxicity and absence of other reasons for concern.

4) No TF decision on need for a Skin Notation

Table 4a: Insufficient Data for TF to reach a decision

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
12	95-50-1	1,2-Dichlorobenzene	Y	N	N			^			
25	109-99-9	Tetrahydrofuran	Y	N	N			^			
29	121-44-8	Triethylamine	Y	N	N			^			

^ Process did not proceed beyond step indicated due to lack of data
Y = Yes
N = No

Comment

For 3 compounds namely tetrahydrofuran (25), 1,2-dichlorobenzene (12), and triethylamine (29) (Table 4A) available data were insufficient to progress beyond step 6 of the ECETOC decision scheme and no recommendation either for a Skin Notation or for no Skin Notation could be made by the TF using the ECETOC strategy. In general no Skin Notation is recommended by the reference countries. Where there is a recommendation for a Skin Notation it is suspected that this has been made on the basis of irritation/corrosivity of the compounds rather than systemic toxicity.

Table 4b: Examination of Gases

No.	CAS No.	Name	Decision steps								Skin Notation
			1	2	3	4	5	6	7	8	
4	74-87-3	Chloromethane	Y	N	N			^			N*
8	75-21-8	Ethylene oxide	Y	N	N			^			N*
30	124-40-3	Dimethylamine	Y	N	N			^			N*

^ Process did not proceed beyond step indicated due to lack of data
* No Skin Notation recommended on the basis that exposure to gases requires a different protection
Y = Yes
N = No

Comment

Chloromethane (4), dimethylamine (30) and ethylene oxide (8) are gases at 15^{o}C. In view of their chemico-physical properties it would be difficult to generate experimental results and it is therefore not surprising that there are no reports of dermal toxicity available indicating that these gases had caused problems due to skin penetration. The TF opinion that Skin Notation is not useful for gases seems to be supported by the reference countries in that no Skin Notation is required in most cases.

4. DISCUSSION AND CONCLUSIONS

For substances that exhibited significant toxicity following dermal absorption there was agreement in assigning a Skin Notation between the ECETOC decision scheme and procedures followed by the reference countries. In other situations, for example where reference authorities were not themselves in agreement, the strategy provided a consistent, scientifically-objective approach drawing upon all relevant information in reaching a conclusion. Although the strategy can operate with a minimum of data, quantitative skin absorption data are of considerable help in the assessment process. Furthermore, in view of the uncertainties in the data and the assumptions made, common sense and experience in the workplace are particularly important when the ratios used in the decision scheme are close to the critical value.

If the ECETOC strategy is regarded as a predictive scheme for the expert judgement of those involved in OEL setting, it is possible to determine its sensitivity and specificity and its positive and negative predictive value.

For those substances where there was sufficient data to use the ECETOC strategy, the sensitivity was 83% (5/6) and the specificity was 100% (6/6) with regard to unanimous decisions. The positive predictive value was 100% (5/5) and the negative predictive value was 86% (6/7).

		Unanimous in 5 Reference Countries	
		Skin Notation	No Skin Notation
ECETOC	Skin Notation	5	0
	No Skin Notation	1	6

The correlation was also good with respect to compounds for which the 5 reference countries were in unanimous (5/5) or majority agreement (4/5). The sensitivity was 88% (7/8) and specificity was 69% (9/13). The positive predictive value was 64% (7/11) and the negative predictive value was 90% (9/10).

		Majority (4/5) in 5 Reference Countries	
		Skin Notation	No Skin Notation
ECETOC	Skin Notation	7	4
	No Skin Notation	1	9

Moreover, in 16 cases where there was no clear consensus between the reference countries on the need for a Skin Notation, the ECETOC strategy gave a clear decision in 13 (81%) cases.

Several general points, relevant to the process of assigning a Skin Notation were identified:

- Carcinogens should not automatically be allocated a Skin Notation (e.g. 1,2-epoxypropane). Carcinogenicity will only play a role in assigning a Skin Notation when skin absorption is important or where skin cancer is considered a relevant end-point.

- The fate of a chemical, once absorbed in the body, may influence the estimation of the contribution to the systemic toxicity dramatically (e.g. ethanolamine). The effects should be judged whether they should be classified as systemic or local (topical).

- Little progress was made in applying the ECETOC strategy to gases (BP <15^{o}C). This was largely due to lack of pertinent data on absorption and systemic toxicity following skin contact. The application of a Skin Notation for a gas would only be effective if it enforced the application of protective measures taking into account the specific nature of the gas e.g. a suit impermeable to gases.(See also Appendix A, Section 2.1: Physical Form of the Substance.) The NOAEL for gases derived from whole body inhalation studies does include contributions to the systemic effects due to the proportion of the gas that penetrated the skin. This indicates that for OELs based on such studies no additional Skin Notation is required. It is recommended that substances likely to be gaseous under ambient conditions be eliminated from further consideration by an initial decision.

- Quantitative skin absorption data are not generally available for corrosive substances. A Skin Notation for such substances is only justified if corrosion occurs as a delayed effect, or in the case of very toxic substances, when absorption through the damaged skin is likely to represent an additional hazard to health.

- The ratio of acute toxicity data for different exposure routes proved crucial in reaching a decision for several substances.

- Low toxicity substances are exempted from a Skin Notation if the numerical values for acute toxicity are above the cut-off values for classification (2000 mg/kg for LD_{50} values, and 200 mg/kg for the calculated $LD_{50\text{ -inh.}}$ values).

- The example of styrene illustrates the general point that a decrease in the OEL value has a major influence on the Critical Absorption Value (CAV) and hence the need for a Skin Notation.

The overall conclusion from this verification exercise with 36 substances is that the strategy as proposed by ECETOC (Appendix A) works well for non-gaseous substances. It is in reasonable agreement with the classifications reached by the reference countries and provides a transparent scheme for future assessments for the necessity of a Skin Notation.

APPENDIX A. STRATEGY FOR ASSIGNING A “SKIN NOTATION”- TEXT OF ECETOC DOCUMENT N° 31 (REVISED)

1. INTRODUCTION

In providing standards for occupational exposure, it has been recognised for a long time that inhalation is not the only route by which a substance can enter the body. In addition to ingestion from contaminated skin, food and smoking materials, absorption through the skin may be particularly important. It is for this reason that lists of Occupational Exposure Limits (OELs) often provide a “skin notation” which indicates that adverse health effects may arise from skin absorption as well as by atmospheric over-exposure.

The criteria that lead to a “skin notation” are generally not specified. An exception is the provisional approach of the Dutch Expert Committee on Occupational Standards (DECOS) which since 1989 has been assessing a semi-quantitative approach to gain experience before committing to a particular method (van Eick and Elskamp, 1989).

In this document, ECETOC has reviewed the factors underlying the criteria and makes proposals which may assist in the achievement of a harmonised approach. The proposals are summarised in a “Decision Tree for Skin Notation” (reproduced as "flip-out" at back of report). It is recommended that this approach be reviewed in the light of experience in use, any formal validation undertaken and any scientific or technical progress.

This revised document No. 31 incorporates the views of a larger circle of people consulted, and especially, the current document accords with the views of The Dutch Expert Committee on Occupational Standards.

2. FACTORS UNDERLYING CRITERIA FOR “SKIN NOTATION”

The purpose of a “skin notation” is to indicate the need to prevent skin contamination when systemic effects may result from percutaneous absorption of the material as a gas, a solid or a liquid. The following factors are involved:

2.1 PHYSICAL FORM OF THE SUBSTANCE

Gases and Vapours

In the majority of cases, percutaneous absorption of gases and vapours is of minor importance in relation to respiratory absorption at occupational exposure levels (NIOSH, 1977). In those few cases where it might be significant - e.g., hydrogen cyanide (Dinman, 1978) and 2-butoxyethanol (Johanson and Bowman, 1991) - gas-tight suits rather than conventional skin protection are necessary since gases and vapours readily penetrate conventional clothing. Gases and volatile liquids with a vapour which can be significantly absorbed through the skin should have OELs set at values where the total absorption (through the respiratory tract and the skin) is not hazardous. For these chemicals a Biological Exposure Limit is a more appropriate standard for workplace exposure control, particularly where there could be exposure to liquid from direct contact or condensation at the skin or clothing.
For chemicals boiling at about ambient temperature (e.g. up to 15° C) surface accumulations are unlikely and liquid material on the skin would evaporate rapidly. Conventional measures following "skin notation" are not sufficient for substances boiling at less than 15° C.

Solids and Liquids

Solids and liquids with a boiling point > 15° C may give rise to skin exposure not only by direct contact but also by impingement of aerosols. The hands, forearms, face and neck (about 3000 cm^2 = 0.3 m^2) confronted with a mean air velocity of 2 km/h sweep a volume of 2000 x 0.3 x 8 m^3 per 8 h shift. This amounts to 4,800 m^3 per shift which is so much greater than the corresponding inhaled volume (conventionally 10 m^3) that low fractional impingement and skin absorption of aerosols may be significant.

It is with these substances that the need for a "skin notation" should be considered.

Ordinary clothing protects the skin temporarily from aerosols and vapour condensate, but as a result of saturation from prolonged use or spillage, it may become a source of skin exposure rather than providing protection against it. It is assumed that good hygiene practices prevent exposure from heavily contaminated clothing and therefore this is not taken into account in considering the need for "skin notation".

2.2 LOCAL VS. SYSTEMIC EFFECTS

For substances which are classified and labelled as skin irritants or sensitisers (e.g. in accordance with Directive 67/548/EEC), good industrial practices and personal protective measures should prevent skin contact. Even when chemicals are encountered as intermediates and therefore there is no container or label, knowledge of the irritant properties should allow practices to be established so that the operators are protected from skin contact. Additional skin protection by the use of a "skin notation" would be redundant if procedural or personal protective measures were always available. Unfortunately, this may not always be true. In addition, certain substances or mixtures of substances show their irritant effects only after a period of delay and so may not provide immediate warning of exposure. Irritant compounds may in addition be toxic systemically. For these reasons classification as irritant or corrosive should not exclude a "skin notation".

2.3 SYSTEMIC TOXICITY

Where the substance is not classified as dangerous in accordance with Directive 67/548/EEC taking into account acute oral, inhalational and dermal effects, chronic effects and the potential for carcinogenicity, mutagenicity and reproductive toxicity and there are no other reasonable grounds for concern, a "skin notation" is considered unnecessary because of insufficient toxicity.

2.4 POTENTIAL FOR PERCUTANEOUS ABSORPTION

If "skin notation" is to be reserved for substances capable of causing systemic effects as a result of skin contact, there must be a potential for percutaneous absorption. The evidence of such absorption can be obtained from the following:

(a) When there is a serious concern based on human case reports/experiences, following careful evaluation of the exposure types mentioned below, the decision to recommend "skin notation" can be taken on the basis of:

- Case reports of systemic effects following skin exposure;
- substantial variation in biological monitoring data in groups with similar inhalational exposure;
- phenomena such as subjective taste after skin (only) exposure and/or odour of the urine after skin (only) exposure;
- experimental studies in man.

(b) Direct measures of percutaneous absorption in human beings or animals using *in vivo* or *in vitro* models.

A word of caution is appropriate in the evaluation of percutaneous absorption data found in the literature, because several orders of magnitude difference sometimes exist between the extreme values reported for one substance. It is recommended that any new studies should be done according to the guideline protocol presented in the ECETOC Monograph on Percutaneous Absorption (ECETOC, 1993).

In the absence of human indirect data or direct experimental data, the possibility of absorption should be estimated by:

(c) inference from the relationship between toxic doses by dermal exposure and toxic doses by other routes.

(c1) The best comparison is between the dermal LD_{50} and the i.v. LD_{50} in order to indicate the extent of percutaneous absorption, except in those cases (e.g., sequestrants*) where the rate of i.v. administration is important. Where the i.v. LD_{50} is not available, the intraperitoneal (i.p.) LD_{50} or a calculated inhalation LD_{50} may be substituted. However the i.p. LD_{50} may be unrepresentative because of partial hepatic metabolism.

The oral LD_{50} should not be used because of the effect of digestion, absorption and hepatic metabolism as well as the absorption rate.

The inhalational LD_{50} can be calculated from the LC_{50} by the formula given by DECOS

$$LD_{50}\text{inhal}[\text{mg/kg}] = \frac{LC_{50}\,[\text{mg/m}^3] \times \text{ventilation rate}[\text{m}^3/\text{h}]\,x\,0.5\,x\,\text{exposure period}[\text{h}]}{\text{body weight}[\text{kg}]}$$

where 0.5 represents a default value for the fractional absorption of inhaled material.

(c2) If the dermal LD_{50} is less than 10 x intravenous LD_{50}, less than 10 x the intraperitoneal LD_{50} or less than 10 x the calculated inhalational LD_{50}, this indicates a significant potential for dermal absorption. However, if the i.v. LD_{50}, the i.p. LD_{50} or the calculated inhalational LD_{50} amount to more than 200 mg/kgbw and the dermal LD_{50} is at least 2,000 mg/kgbw, a ratio of less than 10 should not lead to a “skin notation” (unless the material is classified in respect of chronic, carcinogenic, mutagenic or reproductive effects or would cause other reasonable grounds for

* chelators

concern) because there is no significant toxicity involved. It is not possible to give a comparable criterion for the oral LD_{50} for the reasons given in (c1).

(d) inference from physical/chemical data or structure/activity relationships (SAR).

2.5 COMBINATION OF TOXICITY AND SKIN PENETRATION

A "skin notation" should be applied where the amount absorbed by both hands and forearms in 1 h could amount to more than 10% of the amount that can be absorbed via the lungs on exposure to the OEL for 8 h, *provided that this OEL is set on the basis of systemic toxicity* rather than on sensory or irritant effects or direct effects on the respiratory tract.

In so far as this critical absorption value (CAV) includes all the toxicological data underlying the choice of OEL and skin penetration data, it combines the principles of Sections 2.3 and 2.4.

Assuming that the area of the hands and forearms is 2.000 cm², that a volume of 10m³ is inhaled in 8 hours and that a fraction f (by default assumed to be 0.5) of the atmospheric contaminant is absorbed by the lungs, the 10% criterion (CAV) corresponds to:

$$CAV = \frac{10[m^3] \times OEL\,[mg/m^3] \times f}{2000\,[cm^2]} = \frac{OEL \times f\,[mg]}{2000\,[cm^2]}$$

When $CAV > 0.5 \times f \times OEL\ \frac{\mu g}{cm^2}$ or, using the default value (0.5) for f

when $CAV > 0.25 \times OEL\ \frac{\mu g}{cm^2}$ "skin notation" may be appropriate.

This criterion reflects both cutaneous absorption and toxicity.

Where skin uptake can be quantified and the OEL is set to protect against systemic toxic effects, the condition that the absorption from 2000 cm² skin in 1 h should be less than 10% of the inhaled uptake at the OEL is sufficient. However, when a lower OEL is set to protect from organoleptic, sensory or irritant effects, the "skin notation" may be applied unnecessarily by the use of this criterion. In such circumstances a "systemic" OEL (SOEL) should be developed on the basis of systemic toxicity only and SOEL should be substituted for OEL in the above equation.

For chemicals where there is considerable industrial experience, current best practices and reliable information on health effects from them should be taken into consideration in preference to or along with the theoretical approach.

Bibliography

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ECETOC, 1993. Percutaneous Absorption. Monograph No. 20.

Johanson G and Bowman A, 1991. Percutaneous absorption of 2-butoxyethanol vapour in human subjects. Br. J. Ind. Med. 48, 788.

NIOSH, 1977. Occupational diseases - a guide to their recognition. Department of Health, Education and Welfare, Public Health service, Centre for Disease Control, National Institute of Occupational Safety and Health, 17.

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APPENDIX B. DEFAULT VALUES USED IN APPENDIX C

A. INHALATION RATES FOR DIFFERENT SPECIES

Human (adult)	1 2.50 l/h
Rat (400 g)	7.2 l/h
Mouse	2.0 l/h
Rabbit	36.0 l/h
Guinea pig	8.4 l/h

B. SURFACES OF HUMAN BODY PARTS

Body part	Mean surface area (cm^2)
Total Forearm (plus hand)	1,140
Hands	840
One thumb	40
Total Body	19,400

Total and sub-totals do not reflect the sum of the individual body parts

Reference

Mean surface area by body part for the adult male (EPA, 1989. Exposure Factors Handbook. Office of Health and Environmental Assessment, Exposure Assessment Group, US Environmental Protection Agency, EPA/600/8-89/043, PB90-106774. Washington, DC).

APPENDIX C. DATA SHEETS

1. ANILINE (CAS 62-53-3)

1. Liquid: BP 184.3°C and VP 0.9 kPa at 20 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R48/23/24/25 (Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed)
   - R40 (Possible risks of irreversible effects)
   - R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed).

2. There is circumstantial evidence from human skin exposure indicating a Skin Notation may be required (ILO, 1983).

In addition

3. Experiments in man compared amounts of aniline absorbed by inhalation and dermal contact (Droz *et al*, 1991). Inhalation exposure at 2 ppm (10 mg/m^3), current OEL in some countries, was estimated to result in an uptake of 29 mg/day (50% retention). Infrequent skin contact (one hand, 15 min/day) would yield 72 mg/day and frequent skin contact (2 hands, 2 h/day) 1152 mg/day.

   With the default area for one hand (420 cm^2), both values lead to an hourly absorption rate of
   R = 72 mg/0.25 h/420 cm^2
   = 0.68 mg/cm^2/h

4. OEL (4-10 mg/m^3 ; median, 8 mg/m^3) is based on systemic effects.

5. CAV (10% median OEL = 8 mg/m^3) and the hourly absorption rate compare directly:
   CAV = 0.25 x 8 µg/cm^2/h
   = 2 µg/cm^2/h
   thus R = 0.68 mg/cm^2/h = 340 × CAV.

Comment

Absorption rates through human skin (not measured by a recommended procedure) were found to be 0.2 to 0.7 mg/cm^2/h (Piotrowski, 1957), 0.2-1.22 mg/cm^2/h (solution in water) and 3 mg/cm^2/h (pure liquid) (Dutkiewicz and Piotrowski, 1982).

In the rat, $LD_{50\text{-dermal}}$ = 670 mg/kg (Rehn, 1895) and 4h-$LC_{50\text{-inhal.}}$= 3188 mg/m^3 (DuPont, 1984). Application of the defaults for body weight (0.4kg) and respiratory rate (7.2 l/h) lead to:

$LD_{50\text{-inhal.}}$ = 3188 mg/m^3 x 0.0072 m^3/h x 0.5 x 4 h/0.4 kg = 115 mg/kg

$LD_{50\text{-dermal}}$ = 6 x $LD_{50\text{-inhal.}}$

This again leads to a recommendation for a Skin Notation.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	Yes	Yes	Yes

References

Droz PO *et al*, 1991. Appl. Occup. Environ. Hyg. 6, 465-474.

DuPont de Nemours, 1984. Inhalation median lethal concentration (LC_{50}) for aniline. Haskell Laboratory, Report No. 122-81.

Dutkiewicz T and Piotrowski J, 1982. Experimental investigations on the quantitative estimation of aniline absorption. Pure and Appl. Chem. 3, 319.

ILO (International Labour Office), 1983. Encylopaedia of Occupational Health and Safety, 3rd ed rev., Geneva.

Rehn, 1895. (No title) Arch. Klin. Chir. 50, 588-600.

Piotrowski J, 1957. Quantitative estimation of aniline absorption through the skin in man. J. Hyg. Epidem. Microbiol. Immunol.1, 1-23.

2. MERCAPTOACETIC ACID (THIOGLYCOLLIC ACID: CAS 68-11-1)

1. Liquid: BP 120 °C and VP 0.13 kPa at 60 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed) [due to hypoglycaemic effects caused by the sulphydryl group (Freeman *et al*, 1956)]
   - R34 (Causes burns).

2. No circumstantial evidence from human skin exposure indicating a Skin Notation is required.

3. No human skin absorption data.

6. Rabbit $LD_{50\text{-dermal}}$ (10% acid solution) = 848 mg/kg (95% confidence interval 505-1430 mg/kg) (Dow, 1973).

   Rabbit $LD_{50\text{-iv}}$ = 100 mg/kg (Freeman *et al*, 1956)

   Other LD_{50} values (mg/kg): Rat iv = 114, ip = 70; mouse ip =138, sc = 47, iv =145; guinea pig ip = 157 (listed in RTECS)

   Data for other species and other routes are similar; the rabbit data from Freeman *et al* are considered reliable. The potential for skin absorption is significant since in the rabbit:
   $LD_{50\text{-dermal}} < 10 \times LD_{50\text{-iv}}$

7. The substance is toxic (symbol T) and thus cannnot be excluded on the basis of low toxicity.

Comment

Mercaptoacetic acid is a stronger acid than acetic acid. Due to the corrosiveness of the pure mercaptoacetic acid no data on skin absorption exist. Therefore, a direct assessment of the potential for skin absorption cannot be made for the pure substance. Investigation of the skin absorption of the mercaptoacetate ion was mainly carried out with the sodium or the ammonium salts of the acid which apparently completely dissociate. The substance itself and its salts do not have a skin notation in most of the reference countries, possibly for reason of corrosivity.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	No	No	No	No

References

Dow, 1973. Final Report - Product Safety Testing, Project No. NBS-034, 7-28. The Dow Chemical Co., Environment Health Services, Midland, Michigan.

Freeman MV, Draize JH and Smith PK, 1956. Some aspects of the mechanism of toxicity of thioglycolate. J. Pharmacol. Exp. Ther. 118, 296-303.

3. BENZENE (CAS 71-43-2)

1. Liquid: BP 80.1^{o}C and VP 9.97 kPa at 20^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Classified Category 1 carcinogen
   Risk phrases:
   - R45 (May cause cancer)
   - R48/23/24/25 (Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. Hanke *et al* (1961) reported an hourly absorption of 0.4 mg/cm^2 (400 µg/cm^2/h) when the human forearm was immersed in liquid benzene.

4. OEL is based on systemic effects.

5. CAV is derived from the highest OEL (32 mg/m^3):
   CAV = 0.25 x 32 = 8 µg /cm^2/h
   The measured absorption rate > CAV.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	No	Yes	Yes	Yes	No

Reference

Hanke J, Dutkiewicz T and Piotrowski J, 1961. The absorption of benzene through the skin in men. Med. Pracy 12, 413 -426 (in Polish).

4. CHLOROMETHANE (METHYL CHLORIDE: CAS 74-87-3)

1. Gas: BP -23.7^{o}C

   EC “Classification and Labelling” Directive (67/548/EEC)
   Classified Category 3 carcinogen
   Risk phrases:
   - R40 (Possible risks of irreversible effects)
   - R48/20 (Harmful: danger of serious damage to health by prolonged exposure through inhalation).

2. No circumstantial evidence that chloromethane penetrates human skin; the indication suggested by Mackie (1961) could not be substantiated by other data. The ACGIH Skin Notation is based on a structure-activity relationship to ethyl chloride, methyl bromide and ethyl bromide.

3 No data to show that chloromethane gas specifically penetrates the skin (Appendix A, Section 2.1).

6. Chloromethane is a gas. As would be expected from its physico-chemical properties, there are no data on iv or dermal toxicity .

TF Conclusion

No Skin Notation is recommended on the basis that exposure to gases requires a different protection regime.

ECETOC	ACGIH	D	NL	S	UK
No	Yes	No	No	No	No

Reference

Mackie IJ, 1961. Methyl chloride intoxication. Med. J. Austral. 1, 203-205.

5. ACETONITRILE (CAS 75-05-8)

1. Liquid: BP 80.7°C and VP 10 kPa at 20°C

EC "Classification and Labelling" Directive (67/548/EEC)
Risk phrases:

- R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed).

2. Skin absorption implicated in case of exposure of 2-year-old boy (Caravati and Litovitz, 1988). As inhalation was also possible, no valid conclusion can be drawn.

3. No quantitative skin absorption data were available.

6. Suitable rabbit data were found:

$LD_{50\text{-dermal}}$	1250 mg/kg	Union Carbide (1965)
	5.0 ml/kg (= 3900 mg/kg)	Smyth and Carpenter (1948)
	1.25 ml/kg (= 980 mg/kg)	Pozzani *et al* (1959)
4h-$LC_{50\text{-inhal}}$	2828 ppm = 4750 mg/kg (1ppm = 1.68 mg/m^3)	Pozzani *et al* (1959)

The body weight of the rabbits used by Pozzani *et al* was 2.5 kg (2.16-2.82). The default respiration rate is 36 l/h. With these values the $LC_{50\text{-inhal.}}$ can be converted into an $LD_{50\text{-inhal.}}$ (Appendix A, Section 2.4).

$LD_{50\text{-inhal}} = LC_{50\text{-inhal.}}$ x breath rate x 0.5 x exposure time/body weight
= 4750 mg/m x 0.036 m^3/h x 0.5 x 4 h/2.5 kg
= 137 mg/kg

According to Appendix A, Section 2.4 one criterion for a significant potential for skin absorption is:
$LD_{50\text{-dermal}} < 10 \times LD_{50\text{-inhal.}}$

With the above data the range is:
$LD_{50\text{-dermal}} < (7\text{-}28) \times LD_{50\text{-inhal}}$

The individual data points based on the available acute data are inconsistent

The considerable industrial experience with regard to acetonitrile does not indicate that a Skin Notation is necessary.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

Caravati EM and Litovitz T, 1988. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. J. Am. Med. Assoc. 260, 3470-3473.

Pozzani UC, Carpenter CP, Palm PE, Weil CS and Nair JH, 1959. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1, 634-642.

Smyth HF and Carpenter CP, 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30, 63-68.

Union Carbide, 1965, Data Sheet 3118/65.

6. DICHLOROMETHANE (CHLOROMETHYLENE:CAS 75-09-2)

1. Liquid: BP 40 °C and VP 53.2 kPa at 24 °C

   EC “Classification and Labelling” Directive (67/548/EEC)
   Classified Category 3 carcinogen
   Risk phrase:
   - R40 (Possible risk of irreversible effects).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. In a study, 4 volunteers each immersed one thumb for 1/2 h in 85-88 ml dichloromethane. Inhalation exposure was excluded. The volume displaced/absorbed by the thumbs was 20, 21, and 24 ml. Immediately after the experiment, the concentration of dichloromethane measured in the alveolar air was 3.1 (2.3-3.6) ppm and 0.69 (0.26-1.7) ppm after 2 h. The decrease of the alveolar concentration was exponential (Stewart and Dodd, 1964).

   The total amount of exhaled dichloromethane can be derived from these data and can be converted into an hourly dermal absorption rate R as follows:

   The equation describing the exponential decrease of concentration of dichloromethane in the alveolar air $C_{\mathbf{alveolar}}$ over time t is:
   $C_{\mathbf{alveolar}} = C_0 \times e^{(- k \times t)}$ with the 2 parameters $C_{\mathbf{0}}$ (concentration immediately after experiment at t = 0) and k (describing speed of decrease).
   These parameters are determined by inserting the concentrations at t = 0 and at t = 2h, 3.1 ppm and 0.69 ppm respectively, in the equation:
   $0.69 \text{ ppm} = 3.1 \text{ ppm} \times e^{(- k \times 2h)}$

   Converting this to the logarithm yields k:
   $- k \times 2h = \ln (0.69 / 3.1) = - 1.502$
   $k = 0.751/h$.
   Thus, the decrease of the alveolar concentration, $C_{\mathbf{alveolar}}$ over time is fully described by:
   $C_{alveolar} = 3.1 \text{ ppm} \times e^{(- 0.751/h \times t)}$

1 ppm of dichloromethane converts to 3.37 mg/m^3. For humans, the standard ventilation rate is 1.25 m^3/h. With this, the alveolar air concentration can be converted into the alveolar elimination rate $E_{alveolar}$ of dichloromethane over time:

$E_{alveolar}$ = 1.25 m^3/h x 3.37 mg/m^3/ppm x $C_{alveolar}$

= 13.06 mg/h x $e^{(- 0.751/h \times t)}$

A lower limit for the total amount M_{total} of dichloromethane absorbed is the total amount of dichloromethane exhaled. This amount is received by integrating the elimination rate $E_{alveolar}$ over all times, i.e. between the boundaries t = 0 and t = ∞. The result is:

M_{total} = 13.06 mg/h x [0-1] x (- h/0.751) = 18.31 mg

Standard area of the thumb (40 cm^2) and known immersion time (1/2 h), M_{total} can now be converted to the hourly dermal absorption rate R:

R = M_{total} / 40 cm^2 x 0.5 h

= 18.13 mg / 40 cm^2 x 0.5 h

= 906 µg/cm^2/h

4. OEL (120-360 mg/m^3) is based on systemic toxicity (metabolic conversion of dichloromethane to CO which then binds to haemoglobin).

5. CAV = 1/4 x OEL µg/cm^2/h

= 30-90 µg/cm^2/h

This CAV compares directly with the lower limit for the hourly absorption rate R derived from the data reported from the experiment

R (906 µg/cm^2/h) > CAV (30-90 µg/cm^2/h).

Comment

Taking all the available data into account, R could be about 20 × higher than value derived from the experiment i.e. up to 18,000 (20 x 900) g/cm^2/h. Volunteers, exposed in another experiment for 7.5 h to up to 694 mg/m^3 of dichloromethane, exhaled only 5% of the absorbed amount as dichloromethane, the rest being converted to CO (30%) and (probably) to CO_2 (DiVincenzo and Kaplan, 1981).

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	No	No	No	Yes	No

Experiments in mice seem to confirm this. The absorption rate of liquid dichloromethane was found to be 0.11 mg/cm^2/min = 6,600 g/cm^2/h (Tsuruta, 1975).

References

DiVincenzo GD and Kaplan CJ, 1981. Uptake, metabolism, and elimination of methylene chloride vapor by humans. Toxicol. Appl. Pharmacol. 59, 130-140.

Stewart RD and Dodd HC, 1964. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. Am. Ind. Hygiene Ass. J. 25, 439-446.

Tsuruta H, 1975. Percutaneous absorption of organic solvents 1. Comparative study of the *in vivo* percutaneous absorption of chlorinated solvents in mice. Ind. Hlth. 13, 227-236.

7. CARBON DISULPHIDE (CAS 75-15-0)

1. Liquid: BP 46.3 °C and VP 46.8 kPa at 25 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R48/23 (Danger of serious effects to health by prolonged exposure)
   - R62/63 (Possible risks of impaired fertility and of harm to the unborn child)
   - R36/38 (Irritating to eyes and skin).

2. There is circumstantial evidence on human skin exposure indicating that a Skin Notation may be required (ILO, 1983).

In addition

3. Considerable absorption of CS_2 from liquids was found in two volunteer studies using different methodologies to determine the absorbed CS_2. In both studies, one hand was immersed into an aqueous solution containing 0.33 - 1.67g/l of CS_2.

   In the first study, the quantity of CS_2 absorbed was calculated from the amount exhaled. At 21±1°C the skin absorption rate increased with concentration and was from 21-96 g/cm^2/h. With the solution at 40°C, skin absorption was higher by a factor of 3.1 (Baranowska, 1965).

   In the second study, the quantity of CS_2 absorbed was calculated from the concentration of CS_2 in the solution before and after the experiment. The absorption rate appeared to be about 10 times higher, from 230-790 g/cm^2/h. (Dutkiewicz and Baranowska, 1967).

   Overall, the methodology used in the first study appears more reliable.

4. OEL is 12 - 60 mg/m^3 on the basis of systemic effects.

5. CAV = 0.25 x OEL g/cm^2/h
   = 3-15 g/cm^2/h
   CAV compares directly with the hourly absorption rate from the first experiment:
   R (21-96 g/cm^2/h) = 7-32 x CAV (for the lower limit of the CAV)
   and = 1.5-6.5 x CAV (for the upper limit of the CAV)

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	Yes	Yes	Yes

References

Baranowska B, 1965. Int Arch Gewerbepath Gewerbehyg 21, 362.

Dutkiewicz T and Baranowska B, 1967. The significance of carbon disulphide skin resorption in the evaluation of exposure. In: Brieger H and Teisinger J (ed). Toxicology of Carbon Disulphide, Excerpta Medica Foundation, Amsterdam, 50-51.

ILO (International Labour Office), 1983. Encylopaedia of Occupational Health and Safety, 3rd ed rev., Geneva.

8. ETHYLENE OXIDE (CAS 75-21-8)

1. Gas: BP 13.2 ^{o}C

EC “Classification and Labelling” Directive (67/548/EEC)
Classified Category 2 carcinogen and mutagen
Risk phrases:

- R45 (May cause cancer)
- R46 (May cause heritable effects)
- R23 (Toxic by inhalation)
- R36/37/38 (Irritant to eyes, skin and respiratory tract).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. The substance is a gas, and no data have been found on skin penetration (Appendix A, Section 2.1).

Comment

Conventional measures following Skin Notation are considered insufficient for gases (substances boiling below 15^{o}C (Appendix A, Section 2.1).

TF Conclusion

No Skin Notation is recommended on the basis that exposure to gases requires a different protection regime.

ECETOC	ACGIH	D	NL	S	UK
No	No	Yes	Yes	Yes	No

9. 1,2-EPOXYPROPANE *(*PROPYLENE OXIDE: CAS 75-56-9)

1. Liquid: BP 35 ^{o}C and VP 59 kPa at 20 ^{o}C

   EC “Classification and Labelling” Directive (67/548/EEC)
   Classified Category 2 carcinogen
   Risk phrases:
   - R45 (May cause cancer)
   - R20/21/22 (Harmful by inhalation, by skin contact and if swallowed)
   - R36/37/38 (Irritating to eyes, skin, and the respiratory system).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No skin penetration data.

6. There are data on dermal toxicity data in guinea pigs and rabbits; but these cannot be compared to inhalatory or parenteral toxicity data in the same species as such data do not exist.

   The $LD_{50\text{-dermal}}$ value for guinea pigs and rabbits is 7,168 and 1,244 mg/kg respectively (Hine *et al*, 1956; Smyth, 1969 in BUA-Stoffbericht, 1992).

   The $LC_{50\text{-inhal.}}$ (4 h) in rats and mice is 9,486 and 4,126 mg/m^3 respectively (Jacobson *et al*, 1956). When recalculated to an inhaled dose using the DECOS formula (Appendix A, Section 2.4 (c)), these values correspond to an inhalatory LD_{50} of 341 and 660 mg/kg for rats and mice respectively. Rabbits and monkeys, exposed by inhalation to 1080 mg/m^3 for 278 days, (NOEC), did not show mortality or systemic effects (Rowe *et al*, 1956).

   The calculated LD_{50} > 200 mg/kg but different values of LD_{50}s are > and < 2000 mg/kg. The decision in this case with regard to the Skin Notation could be either "yes" or "no". However although the BP is >15^{0}C, it is nevertheless very volatile and the low dermal LD_{50} values probably reflect the effect of occlusion, not applicable to occupational exposure. Therefore the higher LD_{50} dermal value is accepted.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

BUA- Stoffbericht 94, 1992. 1,2 Propylenoxid, Gesellschaft Deutscher Chemiker .

Environmental Health Criteria 56,1985. Propylene Oxide, IPCS, WHO, Geneva.

Hine CH, Kodama JK, Wellington JS, Dunlap MK and Anderson HH, 1956. The toxicology of glycidol and some glycidyl ethers. Arch. Ind. Hlth. 14, 250-264.

Jacobson KH, Hackley EB and Feinsilver L, 1956. The toxicity of inhaled ethylene oxide and propylene oxide vapors. Arch. Ind. Hlth 13, 237-244.

Rowe VK, Hollingsworth RL, Oyen F, McCollister DD and Spencer HC, 1956. Toxicity of propylene oxide determined on experimental animals. Arch. Ind. Hlth. 13, 228-236.

10. DIMETHYL SULPHATE (CAS 77-78-1)

1. Liquid: BP 188.5 ^{o}C and VP < 0.1 kPa at 20 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Classified Category 2 carcinogen
   Risk phrases:
   - R26 (Very toxic by inhalation)
   - R25 (Toxic if swallowed)
   - R34 (Corrosive).

2. The available human accidental exposure case reports indicate corrosive action on skin and mucosae (Littler and McConnell,1955: Mohlau, 1920).

3. Molodkina *et al* (1979) reported 50% mortality in mice after immersion of the tails in dimethyl sulphate.

6. Yes.

7. No. The substance should not be excluded on the basis of low toxicity (See ***Comment)***.

Comment

No decision can be made concerning the appropriateness of a Skin Notation due to a lack of adequate data, but the severe toxicity (low LD_{50} values and LC_{50} values), delayed corrosivity and carcinogenicity, makes dimethyl sulphate a substance of concern. The mice data indicate that absorption of small quantities of the substance contribute significantly to its systemic toxicity. Therefore a Skin Notation is warranted.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	Yes	No	No

References

Environmental Health Criteria 48, 1985. Dimethyl sulfate. IPCS, WHO, Geneva.

Littler TR and McConnell RB, 1955. Dimethyl sulphate poisoning. Brit. J. lnd. Med. 12, 54-56.

Mohlau FD, 1920. Report of two cases of dimethyl sulphate poisoning. J. Ind. Hygiene Toxicol. 2, 238-240.

Molodkina A NN, Pavlovskaya GS and Dymova EG, 1979. Toxicological and hygienic characteristics of dimethylsulfate production. Gigiena Truda 1 Professional'nykh Zabolevanij 23,28-32 (in Russian).

11. ISOBUTANOL (CAS 78-83-1)

1. Liquid: BP 107.9^{o}C and VP 1.3 kPa at 21.7 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrase:
   - R20 (Harmful by inhalation).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No quantitative data available on the percutaneous absorption of isobutanol in animals.

6. $LD_{50\text{-dermal}}$ in rabbits is 4,240 mg/kg (EHC , 1987)

   Kusheva *et al*, 1983. observed an $LC_{50\text{-inhal.}}$ of 26,250 mg/m^3 in rabbits. This represents an $LD_{50\text{-inhal.}}$ of 630 mg/kg when calculated according to the DECOS proposed formula (Appendix A, Section 2.4(c)).

   The ratio between the $LD_{50\text{-dermal}}$ and the $LD_{50\text{-inhal.}}$ (6.7) is below 10. It must be noted that the $LD_{50\text{-inhal.}}$ is > 200 mg/kg and the $LD_{50\text{-dermal}}$ > 2000 mg/kg indicating isobutanol is of low acute toxicity.

7. Isobutanol shows low acute toxicity for animals.

8. Substance is not classified for long-term or specific effects.

Comment

For n-butanol (an isomer with similar physico-chemical properties) an absorption rate in man of 20 μg/cm^2/h was measured *in vitro* (Grandjean, 1990).

Assuming dermal kinetic behaviour of isobutanol is similar to that of n-butanol,
CAV = 0.25 X OEL μg/cm^2 = 38 μg/cm^2/h,
the absorption rate of isobutanol (20 μg/cm^2/h - in analogy to n-butanol) would be < CAV, indicating there are no reasons for concern.

The available data for isobutanol indicate that systemic effects are unlikely after dermal exposure.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

Environmental Health Criteria 65, 1987. Butanols - four isomers. IPCS, WHO, Geneva.

Grandjean P, 1990. Skin penetration: Hazardous Chemicals at Work, Commission of the European Communities, Taylor and Francis, 52.

Kushneva VS, Koloskova GA, Koltunova JG and Kirilenko VT, 1983. Experimental data for hygienic reglementation of isobutyl alcohol in the working zone. Gigiena Truda 1 Professional'nykh Zabolevanij 1, 46-47.

12. 1,2-DICHLOROBENZENE (CAS 95-50-1)

1. Liquid: BP 180 ^{o}C and VP 0.21 kPa at 25 ^{o}C

   EC “Classification and Labelling” Directive (67/548/EEC)
   Risk phrases:
   - R22 (Harmful if swallowed)
   - R36/37/38 (Irritating to eyes, respiratory system and skin).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No quantitative measurements of dermal absorption in animals.

6. No $LD_{50\text{-dermal}}$ was located, although it has been reported that "five applications to depilated rat skin (painted over an area of 10 cm^2; quantity applied not specified) caused lethal amounts to be absorbed" (Riedel, 1941 in BUA, 1993).

Comment

Data base for 1,2-dichlorobenzene is insufficient.

TF Conclusion

No recommendation can be made regarding the requirement for a Skin Notation.

ECETOC	ACGIH	D	NL	S	UK
No decision	No	Yes	No	No	No

References

BUA, 1993. BUA Report 53,1990. o-Dichlorobenzene (1,2-dichlorobenzene). GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) German Chemical Society/S. Hirzel-Verlag.

13. FURFURAL (CAS 98-01-1)

1. Oily liquid: BP 161^{o}C and VP < 0.2 kPa at 20^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R23/25 (Toxic by inhalation and if swallowed).

2. No circumstantial evidence from human exposures indicating a Skin Notation may be required.

3. Human studies (Flek and Sedivic 1978) indicated that percutaneous penetration following vapour exposure leads to absorption of 20-30% of the amount retained by inhalation.

   During a 15 min liquid contamination of one hand, the same amount was absorbed as would be retained during 8 h inhalation of 10 mg/m^3 . This amount can be quantified as follows:
   Volume inhaled during 8 h is 10 m^3. At an exposure of 10 mg/m^3 the inhalation would be 100 mg. At a retention of 78% this would be 78 mg.

   During 15 min exposure of one hand, approx. 420 cm^2 skin, the estimated absorption being 8 mg furfural. This = 4 x 78/420 = 740 μg/cm^2/h.

   Skin Notification is indicated due to considerable uptake of furfural from the liquid phase through human skin.

   There are no quantitative animal data on the resorption of furfural through the skin.

4. OEL = 10 mg based on systemic toxicity.

5. CAV = 0.5 x 10 x 0.78 = 4 μg/cm^2/h
   Actual absorption of 740 μg/cm^2/h > CAV.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	Yes	Yes	Yes

Reference

Flek J and Sedivic V, 1978. The absorption, metabolism and excretion of furfural in man. Int. Arch. Occup. Hlth. 41, 159-168.

14. ETHYL BENZENE (CAS 100-41-4)

1. Liquid: BP 136 ^{o}C and VP 1.33 pKa at 25.9 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   - R20 (Harmful by inhalation).

2. No circumstantial evidence from human skin exposures indicating that a Skin Notation may be required.

3. In a study on human volunteers no increase in urinary excretion of mandelic acid was observed after 2 h exposure to 650-1300 mg/m^3 (DECOS, 1991). Other studies (Dutkiewicz and Tyzas 1967) using various concentrations of ethylbenzene, indicated that skin absorption increased in a concentration related manner. Concentrations in the range of 11-16% in water lead to skin absorption of 118-216 μg/cm^2/h.

   Supporting data were obtained from in vivo experiments (Susten *et al*, 1990) with hairless mice exposed to radio labelled ethylbenzene. An absorption rate of 2,160 μg/cm^2/h was calculated. In vitro data obtained with rat skin indicate an absorption rate of only 6 μg/cm^2/h (Tsuruta 1982). The human data were considered critical in this assessment.

4. OEL is based on systemic effects.

5. The lowest value in the volunteer-study can be compared directly with the value calculated (Appendix A, Section 2.5) using as a basis 10% resorption during an 8 h exposure at the concentration of the occupational exposure limit (100 ppm). The default factor (50%) is in the range of the experimentally-determined retention factor of the lungs: 49 ± 5% (Gromiec and Pietrowski, 1984).
   CAV = 0.25 x 435 μg/cm^2/h = 109 μg/cm^2/h.

   The lower value for skin absorption (118 μg/cm^2/h) from the volunteer-studies using dilute aqeuous ethylbenzene is slightly more than the CAV of 109 μg/cm^2/h. Greater absorption may be predicted after dermal exposure to pure ethylbenzene or more concentrated solutions.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	No	Yes	Yes	No	No

References

DECOS, 1991. Health based recommended occupational exposure limit for ethylbenzene (RA 9/91). Ministry of Social Affairs and Employment, Labour Inspectorate, The Hague, NL.

Dutkiewicz T and Tyzas H, 1967. A study of the skin absorption of ethylbenzene in man. Brit. J. Ind. Med. 24, 330-345.

Gromiec JP and Pietrowski JK, 1984. Int. Arch Occ Env Hlth 55, 61-72.

Susten AS, Niemeier RW and Simon SD, 1990. In vivo percutaneous absorption of volatile organic solvents in hairless mice. II Toluene, ethylbenzene and aniline. J. Appl. Toxicol. 10, 217-225.

Tsuruta H, 1982. Percutaneous absorption of organic solvents. III On the penetration rates of hydrophobic solvents through the excised rat skin. Ind. Hlth. 20, 335-345.

15. STYRENE (CAS 100-42-5)

1. Liquid: BP 145.5°C and VP 1.33 pKa at 30.8 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R20 (Harmful by inhalation)
   - R36/38 (Irritant to eyes and skin).

2. No circumstantial evidence on human skin exposure indicating a Skin Notation may be required.

3. Experimental studies with human volunteers provide quantitative data on dermal absorption. Berode *et al* (1985) measured dermal uptake in 9 male volunteers who dipped one hand in liquid styrene. A mean value of 1 μg/cm^2/min was obtained; this is equivalent to 60 μg/cm^2/h.

   The experimentally-determined retention factor for man is 59-88% (Fiserova-Bergerova and Teisinger, 1965; Barodej and Bardodejova, 1970; Fernandez and Caperos, 1977; Kjellberg *et al*, 1979; Norström *et al*, 1992).

4. OEL is based on systemic effects (neurotoxicity).

5. Dermal absorption for styrene can be compared with CAV.

   Published occupational exposure standards for styrene among the reference countries range from 420 mg/m^3 (UK, NL), through 215 mg/m^3 (USA) to 90 mg/m^3 (D, S).

   CAV calculated for different OELs using a retention factor (Rf) of 0.59 or 0.88 is:

OEL in mg/m^3 (ppm)	Calculated CAV	
	Rf = 0.59	Rf = 0.88
420 (50)	123.9	184.8
215 (25)	63.4	94.6
90 (10)	26.6	39.6

Dermal absorption of liquid styrene (60 μg/cm^2/h) < CAV where OEL= 420 mg/m^3 and 215 mg/m^3 but > CAV where OEL = 90 mg/m^3.

Comment

Most countries have an OEL for styrene of 215 mg/m^3 (50 ppm) or higher. At this level, skin absorption is lower than the CAV and no skin notation is recommended. At a lower OEL, however, dermal absorption will contribute a greater proportion of the allowed uptake.

These calculations demonstrate the need for an accurate measurement of lung retention, since dermal absorption may become relatively of greater importance when uptake by inhalation is low.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	Yes*	No	No	Yes^	No

* TLV = 50 ppm

^ TLV = 20 ppm

References

Barodej Z and Bardodejova E, 1970. Biotransformation of ethyl benzene, styrene and alpha-methyl styrene in man. J. Am. Ind. Hyg. Assoc. 31, 206-209.

Berode M, Droz P-O and Guillemin M, 1985. Human exposure to styrene VI Percutaneous absorption in human volunteers. Int. Arch. Occup. Environ. Hlth. 55, 331-336.

Fernandez JG and Caperos JR, 1977. Styrene exposure. 1. An experimental study of pulmonary absorption and excretion in humans. Int .Arch. Occup. Environ. Hlth. 40, 1-12.

Fiserova-Bergerova V and Teisinger J, 1965. Pulmonary styrene vapour retention. Ind. Med. Surg. 34, 620-622.

Kjellberg A, Wigaeus E, Engstrom J, Cstrand I and Ljungquist E, 1979. Long term effects of exposure to styrene in a polyester plant. Arbete Och Hälsa 18, 55-67.

Norström A, Lof A, Aringer L, Samuelsson R, Andersson B, Levin JO and Naslund P, 1992. Determination of N-acetyl-S-(2-phenyl-2-hydroxyethyl)cysteine in human urine after experimental exposure to styrene. Chemosphere 24, 1553-1561.

16. 4,4'-DIAMIN0-3,3'-DICHLORODIPHENYLMETHANE (MBOCA; *2,2'*-DICHLORO-4,4'-METHYLENEDIANILINE; 4,4'-METHYLENEBIS (2-CHLOROANILINE): CAS 101-14-4)

1. Solid

   EC "Classification and Labelling" Directive (67/548/EEC)
   Classified Category 2 carcinogen
   Risk phrases:
   - R45 (May cause cancer)
   - R22 (Harmful by ingestion).

2. Biological monitoring indicated that routes other than inhalation contribute to absorption but the importance of these is not known: only qualitative human data are available (Ishikawa *et al*, 1990). An accidental spill with molten MBOCA on human skin has been described (Osorio *et al*, 1990): MBOCA was present in urine (1700 ppb after 4 h) and disappeared after 4 days. Ingestion apparently did not take place but inhalation of vapour may have been a contributing factor.

3. Absorption, tested *in vitro* with isolated human neonatal skin (Ishikawa *et al*, 1990) was in the range of 0.07- 0.3 mg/cm^2/h.

4. OEL of 0.005-0.22 mg/m^3 is established in different countries based on the carcinogenic potential of MBOCA.

5. CAV is 0.06-0.001 mg/cm^2/h, depending on the OEL value.

   The lowest absorption rate determined by Ishikawa *et al* is 0.07 mg/cm^2/h which exceeds both CAV values.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	No	Yes	No	Yes

References

Ishikawa Y, Yoshida M, Okayama A, Hara I and Morimoto K, 1990. Biological monitoring for workers exposed to 4,4'-methylenebis(2-chloroaniline). J. Am. Lnd. Hyg. Assoc. 51, 5-7.

Osorio AM, Clapp D, Ward E, Wilson HK and Cocker J, 1990. Biological monitoring of a worker acutely exposed to MBOCA. Am. J. lnd. Hyg. 18, 577-589.

17. 4,4'-METHYLENEDIANILINE (MDA: CAS 101-77-9)

1. Crystalline solid: MP 90 ^{o}C

EC “Classification and Labelling” Directive (67/548/EEC)
Classified as Category 2 carcinogen
Risk phrases:

- R45 (May cause cancer)
- R20/21/22 (Harmful by inhalation, skin contact and if swallowed)
- R48/20/21 (Danger of serious damage to health by prolonged exposure through inhalation and contact with skin)
- R43 (May cause sensitisation by skin contact).

2. Human experience indicates that skin penetration is important:

McGill and Moto (1974) reported jaundice in 12/100 workers engaged in the manufacture of insulation material containing MDA, skin being the major exposure route.

Williams *et al* (1974) reported acute hepatitis in 6/300 workers who had been coating walls with epoxy mixtures containing MDA. No air concentrations were given, but there was ample opportunity for skin absorption.

A worker exposed to MDA following the malfunction of a filter system developed transient signs of hepatic and myocardial damage. Exposure was both by inhalation and skin contact (amounts, exposure levels not stated) (Brooks *et al*, 1979).

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	No	No	No

References

Brooks LJ *et al,* 1979. Acute myocardiopathy following tripathway exposure to methylenedianiline. J. Am. Med. Assoc, 242, 1527.

Hathaway JA, Aubrun J-CP and Leplay A, 1992. Medical surveillance for 4,4' -methylenedianiline. Proceedings of the Conference on advanced composites. American Conference Governmental Industrial Hygienists.

McGill DS and Moto JD, 1974. An industrial outbreak of toxicity hepatitis due to methylenedianiline. New Eng. J. Med. 291, 278.

Williams GW *et al* ,1974. Toxic hepatitis and methylenedianiline. New Eng. J. Med. 291, 1256.

18. 1,2-EPOXY- 4-EPOXYETHYLCYCLOHEXANE (VINYLCYCLOHEXENE DIEPOXIDE: CAS 106-87-6)

1. Liquid: BP 227 °C and VP < 0.1 kPa at 20 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R40 (Possible risk for irreversible effects)
   - R23/24/25 (Toxic by inhalation, skin contact and if swallowed).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No quantitative skin absorption data available.

6. Repeat exposure dermal toxicity studies showed systemic effects in rodents at relatively low doses. Uterine/ovarian atrophy was reported for mice given 62 mg/kg. Survival in rats was adversely affected at 50 mg/kg. In both studies dermal applications took place over the lifetime of the animals. Systemic effects were observed in these species at higher doses in a preliminary 13-week study (NTP, 1989). Data from a study in the rabbit are available to allow a comparison of toxicity after administration by different routes:

   $LD_{50\text{-dermal}}$ (rabbit) = 680 mg/kg (Weil *et al*, 1963)
   $LC_{50\text{-inh.}}$ = 4,560 mg/m^3 (Shell, 1961); the calculated $LD_{50\text{-inh.}}$ = 164 mg/kg.

   The ratio $LD_{50\text{-dermal}}$/ $LD_{50\text{-inh.}}$ = 4.1, which is < 10.

7. No. The substance cannot be excluded on the basis of low toxicity.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	No	No	No	No

References

National Toxicology Programme (NTP), 1989. Toxicology and carcinogenicity studies of 4-Vinyl-1-cyclohexene diepoxide in F344/N rats and B6C3F1 mice. Technical Report Series N362, No. 90-2817, NTS Pub. No. PB-90-219-957, Springfield, VA.

Weil CS *et al*,1963. Experimental carcinogenicity and acute toxicity of representatives epoxides. J. Am. Ind. Hyg. Assoc. 24, 305-325.

Shell Chemical Co.,1961. Unpublished report.

19. 1-ALLYL-2,3-EPOXYPROPYL ETHER (ALLYLGLYCIDYL ETHER: CAS 106-92-3)

1. Liquid: BP 154 ^{o}C and VP 0.6 kPa at 25^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R20 (Harmful by inhalation)
   - R43 (May cause sensitisation by skin contact).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No information on skin absorption rates in animals or man.

6. $LD_{50\text{-dermal}}$ (rabbits) = 2,550 mg/kg (Hine *et al*, 1956).

   $LC_{50\text{-inh.}}$ is 3,082 mg/m^3 in rats and 1,242 mg/m^3 in mice (Hine *et al*, 1956).

   Calculated $LD_{50\text{-inh.}}$ are respectively 222 mg/kg and 200 mg/kg for rats and mice.

   This results in a $LD_{50\text{-dermal}}/LD_{50\text{-inh.}}$ marginally > 10.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	Yes	No	Yes

Reference

Hine GH, Kodama JK and Wellington JS, 1956. The toxicology of glycidol and some glycidyl ethers. Arch. Ind. Hlth. 14, 250-267.

20. 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE: CAS 107-06-2)

1. Liquid: BP 83 ^{o}C and VP 10 kPa at 20 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Classified Category 2 carcinogen
   Risk phrases:
   - R45 (May cause cancer)
   - R22 (Harmful if swallowed)
   - R36/37/38 (Irritating to skin, eyes and respiratory tract).

2. No circumstantial evidence from human skin exposure indicating that a Skin Notation may be required.

3. A dermal penetration rate for mouse skin *in vivo* was 479 nmol/cm^2/min (Tsuruta, 1975) and for rat skin *in vitro* was 169 nmol/cm^2/min (Tsuruta, 1977). Blood concentrations of 1,2-dichloroethane have also been reported to increase rapidly in the guinea pig after dermal application (Jakobson, 1982). Systemic effects were reported in rabbits treated dermally with dichloroethane (Petrun and Proklina, 1967).

   Dermal penetration rate of 479 nmol/cm^2/hour is equivalent to 2874µg/cm^2/h.
   R = 2874µg/cm^2/h.

4. OELs are based on systemic effects and a typical value is 20 mg/m^3

5. CAV = 5µg/cm^2/h
   R>>CAV

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	No	No	No	Yes	No

References

DuPont de Nemours, 1981. Haskell Laboratory, Report No 699-81.

Jakobson I, Wahlberg JE, Holmberg B and Johansson G, 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol. Appl. Pharmacol. 63, 181-187.

McCollister DD, Hollingsworth RL, Oyen F and Rowe VK, 1956. Comparative inhalation toxicity of fumigant mixtures. Individual and joint effects of ethylene dichloride, carbon tetrachloride and ethylene dibromide. Arch. Ind. Hlth. 13, 1-7.

Petrun NM and Proklina TL, 1967. Farmokol. Toksikol. 30, 356-358.

Smyth HF, Carpenter CP, Weil CS, Pozzani UC, Striegel SA and Nycum JS, 1969. Range-finding Toxicity Data: List VII. J. Am. Ind. Hyg. Assoc. 30, 470-476.

Tsuruta H, 1975. Percutaneous absorption of organic solvents. I. Comparative study of the in vivo percutaneous absorption of chlorinated solvents in mice. Ind. Hlth. 13, 227-236.

Tsuruta H, 1977. Percutaneous absorption of organic solvents. II. A method for measuring the penetration rate of chlorinated solvents through excised rat skin. Ind. Hlth. 15, 31-139.

21. ETHYLENE GLYCOL (EG; 1,2-ETHANEDIOL: CAS 107-21-1)

1. Liquid: BP 197 ^{o}C and VP < 0.1kPa at 20 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrase:
   - R22 (Harmful by ingestion).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation is required.

3. No quantitative measurements of dermal absorption in animals.

6. A dermal LD_{50} of 10.6 g/kg has been reported for rabbits (Union Carbide, 1958, in BUA, 1993) suggesting some potential for skin absorption. An $LD_{50\text{-iv.}}$ of 4.4 - 5.0 g/kg has also been reported for this same species (Hanzlik *et al,* 1931, in BUA ,1993).

   These observations suggest a significant potential for absorption following skin contact, since the dermal LD_{50} < 10-fold the $LD_{50\text{-iv..}}$ However, the $LD_{50\text{-iv.}}$ > the default limit value of 200 mg/kg, and the $LD_{50\text{-dermal}}$ > the 2,000 mg/kg default, indicating that skin absorption of ethylene glycol should be considered insignificant.

7. Yes, the substance can be excluded on the basis of low toxicity.

8. No, the substance should not be classified for long-term or serious health effects.

TF Conclusion

No Skin Notation recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

Reference

BUA, 1993. Ethylenglykol (1,2-ethandiol), BUA-Stoffbericht 92 (Juni 1991), S. Hirzel Verlag, Stuttgart, Germany.

22. 1-METHOXYPROPANOL-2 (2-PG-1-ME: CAS 107-98-2)

1. Colourless liquid: BP 120 ^{o}C and VP 1.2 kPa at 20 ^{o}C

   Not classified as dangerous to health according to EC "Classification and Labelling" Directive (67/548/EEC).

   A review of available toxicity data (ECETOC, 1995) indicates that for 2PG-1-ME:

   $LD_{50\text{-oral}}$ > 2,000 mg/kg

   $LD_{50\text{-dermal}}$ > 2,000 mg/kg

   $LC_{50\text{-inhalation}}$ > 135 mg/l in 4 h

   2PG-1-ME is:

   - non irritant to skin or eyes,
   - not a sensitiser,
   - non genotoxic,
   - not toxic to reproduction,
   - not toxic to the haematopoietic system.

Comment

These characteristics, in particular the $LD_{50\text{-dermal}}$ data (> 2,000 mg/kg) indicate no Skin Notation is necessary, even though *in vitro* studies suggest that dermal penetration is possible (Dugard *et al*, 1984).

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	Yes

References

ECETOC, 1995. The toxicology of glycol ethers and its relevance to man. Technical Report No. 64.

Dugard PH, Walker M, Mawdsley SJ and Scott RC, 1984. Absorption of some glycol ethers through human skin *in vitro*. Environ. Hlth. Persp. 57, 193-197.

23. METHYL ISOBUTYL KETONE (MIBK; 4-METHYL-2-PENTANONE: CAS 108-10-1)

1. Flammable liquid: BP 117.5 °C, and VP 0.97 pKa at 25 °C

Not classified as dangerous to health according to EC "Classification and Labelling" Directive (67/548/EEC).

A review of available toxicity data (ECETOC, 1987) confirms that MIBK does not require classification for systemic toxicity :

$LD_{50\text{-oral}}$ >2,000 mg/kg

$LD_{50\text{-dermal}}$ >2,000 mg/kg

$LC_{50\text{-inhalation}}$ 20,000 mg/m^3

MIBK :

- is not genotoxic;
- is not teratogenic or embryotoxic at sub-maternally-toxic exposure levels;
- has some potential to cause eye irritation, but this effect alone is not relevant to assigning a skin notation.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	Yes

Reference

ECETOC, 1987. Methyl isobutyl ketone (CAS 108-10-1). JACC Report No.8.

24. ISOBUTYL METHYLCARBINOL (4-METHYL-2-PENTANOL; METHYL ISOBUTYL CARBINOL; MIC: CAS 108-11-2)

1. Flammable liquid: BP 132 ^{o}C and VP 0.45 kPa at 20^{o}C

   Not classified as dangerous to health according to EC "Classification and Labelling" Directive 67/548/EEC.

2. No circumstantial evidence on human skin exposure to indicate that a Skin Notation is required.

3. No skin penetration data are available.

6. $LD_{50\text{-dermal}}$ in rabbits is 2,876 mg/kg (Smyth *et al*, 1951) with little or no potential to cause skin irritation. $LC_{50\text{-inh.}}$ > 4,000 ppm for 2 h or < 2,000 ppm for 8 h (Smyth *et al*, 1951). The $LD_{50\text{-inh.}}$ calculated according to the DECOS formula is 344-600 mg/kg (average, used in the ratio below is 400 mg/kg)
   Ratio $LD_{50\text{-dermal}}/LD_{50\text{-inh.}}$ = 7

7. $LD_{50\text{-dermal}}$ > 2,000 mg/kg.

8. Substance does not need to be classified for serious long-term or specific health effects.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	Yes	Yes	Yes	Yes	Yes

Reference

Smyth HF, Carpenter C P and Weil C S, 1951. Range-finding toxicity data, list IV. Arch. Ind. Hyg. Occup.Med. 4, 119-220.

25. TETRAHYDROFURAN (CAS 109-99-9)

1. Highly flammable liquid: BP 66 ^{o}C and VP 20 kPa at 20 ^{o}C

   EC “Classification and Labelling” Directive(67/548/EEC)

   Risk phrases:

   - R36/37 (Irritating to eyes and respiratory tract).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation is required.

3. No quantitative data on skin penetration.

6. No information to allow comparison through various routes of exposure.

TF Conclusion

Data are insufficient to decide on the requirement for a Skin Notation.

ECETOC	ACGIH	D	NL	S	UK
No decision	No	No	No	No	No

26. n-HEXANE (CAS 110-54-3)

1. Liquid: BP 68.95 °C and VP 18 kPa at 20 °C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R48/20 (Danger of serious damage to health after prolonged exposure).

2. No. [There are only isolated reports implicating dermal absorption. Skin absorption of n-hexane has been implicated in a case report on peripheral neuropathy (Nomiyama *et al* 1973). Severe neuropathy was also found in a young girl who, in addition to moderate exposure by inhalation, had had occupational skin contact with n-hexane lasting several hours every day (Takahashi *et al,* 1977)].

3. Skin absorption in humans has not been observed. A limited study, which cannot be considered definitive, was carried out on a volunteer who immersed one hand in n-hexane for 1 min; no n-hexane was found in the blood or in the exhaled air (Nomiyama and Nomiyama, 1975).

   Skin absorption in animals is low. For guinea pigs (0.6-1 kg), exposed dermally for 30 min to n-hexane (skin contact area 12.4 cm^2) the peak blood concentration was 0.58 g/ml (Jakobson *et al*, 1982). This can be converted into an hourly absorption rate, assuming a blood volume of 56 ml (equivalent to 70% of the average body weight of 0.8 kg):
   R (guinea pig) = 0.58 μg/ml x 56 ml / 12.4 cm^2 / 0.5 h = 5.2 μg/cm^2/h.

   Tsuruta (1982) found a penetration rate of 0.0118 nmol/cm^2/min for rat excised skin. With the molecular weight of 86.17 g/mol this is equivalent to an hourly penetration rate of:
   R (excised rat skin) = 0.0118 nmol/cm^2/min x 60 min/h x 86.17 g/mol = 0.06 μg/cm^2/h.

4. OEL (70-180 mg/m^3) is based on systemic effects due to metabolic conversion of n-hexane to 2,5-hexanedione, a potent neurotoxicant.

5. CAV = 0.25 x OEL μg/cm^2/h = 17.5 to 45 μg/cm^2/h
   Comparison of the CAV with dermal absorption data for the rat and the guinea pig demonstrated that:
   R ≈ 0.3 x CAV (guinea pig)
   R ≈ 0.0034 x CAV (excised rat skin)

Comment

Although for the guinea pig R > 0.25 CAV in view of the fact that the R is a calculated value and marginally > 0.25 CAV, the conclusion is that R is not greater than 0.25 CAV.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

Jakobson I, Wahlberg JE, Holmberg B and Johansson G, 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anaesthetised guinea pigs. Toxicol. Appl. Pharmacol. 63,181-187.

Nomiyama K and Nomiyama H, 1975. Concerning the cutaneous absorption of n-hexane in humans. Japan J. Hyg. 30, 140 (in Japanese).

Nomiyama K, Yoshida T and Yanagisawa H, 1973. Percutaneous absorption of n-hexane caused severe polyneuropathy. In: Proc. of the 46th Ann. Meeting of the Japanese Association of Industrial Health, Tokyo. Japan Ass. Ind.Hlth., 560-561 (in Japanese).

Takahashi M, Takeuchi H, Kyo S, Yorifuji S, Sanagi SL, Seki Y and Hara I, 1977. n-Hexane poly-neuropathy: a case report with review of literature. Med. J. Osaka Univ 28, 77-85.

Tsuruta H, 1982. Percutaneous absorption of organic solvents. Ill. On the penetration rates of hydrophobic solvents through the excised rat skin. Ind. Hlth. 20, 335-345.

27. DIETHYLENE TRIAMINE (CAS 111-40-0)

1. Liquid: BP 200 ^{o}C and VP < 0.1 kPa at 20 ^{o}C

   EC “Classification and Labelling” Directive (67/548/EEC)

   Risk phrases:

   - R21/22 (Harmful by inhalation and skin contact)
   - R34 (Causes burns)
   - R43 (May cause sensitisation by skin contact).

2. No circumstantial evidence on human skin exposures indicating that a Skin Notation may be required.

3. No skin penetration data.

6. Dermal toxicity data indicate the potential to cause harm following skin contact.

   $LD_{50\text{-dermal}}$ (rabbit) = 1,090 mg/kg; (guinea pig) 162 mg/kg.

7. Substance cannot be excluded on the basis of low toxicity.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Not listed	Yes	Yes	Yes

28. 2-BUTOXYETHANOL (2BE: CAS 111-76-2)

1. Liquid: BP 171 ^{0}C and VP 0.1 kPa at 25 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R37 (Irritating to the respiratory system)
   - R20/21/22 (Harmful by inhalation, in contact with the skin and if swallowed).

2. Clinical and volunteer studies demonstrated that dermal absorption was possible, but with no associated adverse health effects (ECETOC, 1994).

In addition

3. Experimental studies with human volunteers provided quantitative data on dermal absorption. Johanson *et al* (1988) measured dermal uptake in volunteers following immersion of 2 or 4 fingers in liquid 2BE. A mean value of 20 nmol/cm^2/min (2.36 µg/cm^2/min) was determined, equivalent to 142 µg/cm^2/h.

4. Intravascular haemolysis of erythrocytes is the critical toxic effect in animal studies, but this is seen in man only after over-exposure following deliberate ingestion of products containing 2BE (ECETOC, 1994). Workplace exposure standards have been devised primarily to protect against respiratory irritation while minimising the potential risk of haematological effects.

5. The value of 142 µg/cm^2/h can be compared directly with the outcome of the application of the formula in Appendix A, Section 2.5, calculating 10% of the amount absorbed during inhalation exposure at an occupational exposure standard of 100 mg/m^3. The experimentally-determined inhalation retention factor for man is 57% (Johanson *et al*, 1986 and 1991).

   CAV = 0.5 x 0.57 x 100 = 28.5 µg/cm^2
   Dermal absorption of 2BE liquid (142 µg/cm^2/h) > CAV (28.5 µg/cm^2).

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	Yes	Yes	Yes	Yes

References

Carpenter CP, Pozzani UC, Wiel CS, Nair JH, Keck GA and Smyth HF, 1956. The toxicity of butyl cellulose solvent. AMA Arch. Ind. Hlth. 14, 114-131.

ECETOC, 1994. Butoxyethanol criteria document, including a supplement for 2-butoxyethyl acetate. Special Report No.7.

Johanson G, Kronberg H, Naslund PH and Nordqvist B, 1986. Scand. J. Work. Environ. Hlth. 12, 594-602.

Johanson G, Boman A and Dynesius B, 1988. Percutaneous absorption of 2-butoxyethanol in man. Scand. J. Work Environ. Hlth. 14, 101-109.

Johanson G and Boman A, 1991. Percutaneous absorption of 2-butoxyethenol vapour in human subjects. Br J Ind Med 48, 788-792.

29. TRIETHYLAMINE (CAS 121-44-8)

1. Liquid: BP 88.8^{o}C and VP 7kPa at 20^{0}C

   EC "Classification and Labeling" Directive (67/548/EEC)
   - R36/37 (Irritating to eyes and skin).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No quantitative measurements of dermal absorption in animals.

6. Health effects information on the material is limited, with no reports of systemic or organ-related toxicity. A single dermal LD_{50} value of 0.57 ml/kg (equivalent to 410 mg/kg) is reported for the rabbit (Benya and Harrison, 1994) suggesting some potential for harm following skin contact. The original report of this work was unavailable and it is not possible to determine if death was due to systemic effects or was secondary due to dermal corrosion.

TF Conclusion

Insufficient data available to decide on the requirement for a Skin Notation.

ECETOC	ACGIH	D	NL	S	UK
No decision	Yes	No	Yes	No	No

Reference

Benya TJ and Harrison RD, 1994. Aliphatic and alicyclic amines. In Patty's Industrial Hygiene and Toxicology, 4th edition, Vol. IIB. Ed Clayton, GD and Clayton, FE. J Wiley and Sons, NY.

30. DIMETHYLAMINE (CAS 124-40-3)

1. Highly flammable gas: BP 7 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R36/37 (Irritant to eyes and respiratory system).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. No skin penetration data.

6. $LD_{50\text{-inh.}}$ can be estimated using the DECOS formula:
   $LD_{50\text{-inh.}} = LC_{50\text{-inh.}}$ x ventil. rate x fraction absorbed x exp.time/ bdw.= 312 mg/h
   Substituting the relevant values including the $LC_{50\text{-inh.}}$ of 8,666 gives an $LD_{50\text{-inh.}}$ of 312 mg/h (Steinhagen *et al*, 1982).
   In the absence of a dermal LD_{50} the dermal toxicity and the toxicity by inhalation cannot be compared.

Comment

Dimethylamine is a gas. As would be expected from its physico-chemical properties there are no data on iv or dermal toxicity.

TF Conclusion

No Skin Notation is recommended on the basis that exposure to gases requires a different protection regime.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

Notice of intended change, 1992. Dimethylamine. Appl. Occup. Environ. Hyg., 59-61.

Steinhagen WH, Swenberg JA and Barrow CS, 1982. Acute inhalation toxicity and sensory irritation of dimethylamine. J. Am. Ind. Assoc. 43, 411-417.

31. TETRACHLOROETHYLENE (CAS 127-18-4)

1. Colourless liquid: BP 121^{o}C and VP 0.78 kPa at 25^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Classified Category 3 carcinogen.
   Risk phrase:
   - R40 (possible risks of irreversible effects).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required.

3. McDougal *et al* (1990) quantified absorption of vapour by the human skin *in vivo* as 54 μg/cm^2/h. Absorption of liquid after direct skin contact was not measured, but can be deduced as follows:

   Stewart and Dodd (1964) immersed a volunteer's thumb (40 cm^2) for 30 min in tetrachloroethylene. The maximum concentration in exhaled air during the immersion and continuing for 2.5 h following the immersion was 2.1 mg/m^3. Assuming a constant excretion for 2.5 h at half (1.05) of the peak concentration (1.05 mg/m^3) and assuming the exhaled volume during this time to be 3.125 m^3 (2.5x 10m^3/ 8 - the mean inhalation volume of humans/h) then the exhaled quantity can be calculated as 3.125 x 1.05 = 3.3 mg. This is estimated to be the amount absorbed through the skin of the thumb during the 0.5 h immersion.
   This equates to: 3300 x 2/40 μg/cm^2/h= 165 μg/cm^2/h .

4. OEL is based on systemic toxicity.

5. The most frequently-used OEL is 340 mg/m^3.
   CAV = 0.25 x 340 = 85 μg/cm^2/h.

Comment

The indirect evidence for the need of a skin notification leads to a marginally higher absorption rate of twice the CAV. The margin increases with the current trend to decrease the OEL for the substance.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	No	No	Yes	Yes	No

References

ECETOC. Tetrachloroethylene (CAS 127-18-4). JACC Report. In preparation.

McDougal JM *et al*, 1990. Dermal absorption of organic chemical vapours in rats and humans. Fund Appl. Toxicol., 14, 299-308.

Stewart RD and Dodd HC, 1964. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin. J. Am. Ind. Hyg. Assoc. 25, 439-446.

32. ETHANOLAMINE (CAS 141-43-5)

1. Colourless liquid: BP 170 ^{o}C and VP < 0.1 kPa at 20 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R20 (Harmful by inhalation)
   - R36/37/38 (Irritating to eyes, respiratory system and skin).

2. No circumstantial evidence on human skin exposure indicating that a Skin Notation may be required

   Paustovskaya *et al* 1973 suggested that ethanolamine may be absorbed through the skin.

3. Klain *et al* (1985) in radio-labelled studies in mice concluded that ethanolamine slowly penetrated the epidermis. A significant amount remained topical and was incorporated into phospholipids. In this bounded form ethanolamine cannot contribute to the systemic toxicity. A quantitative penetration rate expressed in μg/cm^2/h could not be calculated from these data.

   Skin penetration data are available from a comparative *in vitro* study using radio-labelled ethanolamine on skin samples of rat, mice, rabbit and man (Beskitt *et al*, 1993). The penetration rate for human skin was 9.7 μg/cm^2/h . The amount retained in the skin after 24 h was 10 fold 0.06% of the dose found in the effluent.

4. The OEL of 3 ppm (7.5 mg/m^3) commonly used in all reference countries is based on systemic toxic effects. This allows a direct comparison of resorption rate and OEL. In the absence of experimental data on the retention by the lungs, a default factor of 0.5 was used following the formula in Appendix A, Section 2.5.

5. CAV = 0.25 x 7.5(OEL) μg/cm^2/h = 1.87μg/cm^2/h. The measured penetration rate of 9.7 μg/cm^2/h > CAV.

Comment

In view of the kinetic and metabolism data developed by Klain *et al* (1985) for mice skin and by Beskitt *et al* (1993) for skin samples of rats, mice, rabbits and human, indicating that significant retention and metabolism takes place in the skin, skin notation is considered unnecessary.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	No	No	No

References

Paustovskaya VV *et al*, 1973. Gig. Truda Prof. Zabol 9, 34 (Chem Abs 85, 12977 t)

Beskitt JL, Sun JD and Tallant MJ, 1993. Diethanolamine (DEA) and monoethanolamine (MEA): Species comparisons of in vitro skin penetration following a single application to the female skin of humans, rats, mice and rabbits. Draft report Bushy Run Research Center, project 91 No144.

Klain GJ, Reifenrath WG and Black KE, 1985. Distribution and metabolism of topically applied ethanolamine. Fund Appl. Toxicol., 127-133.

33. 1,3-DICHLOROPROPENE (1,3-DCP: CAS 542-75-6)

1. Liquid: BP 108^{o}C and VP 3.7 kPa at 20^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R25 (Toxic if swallowed)
   - R20/21 (Harmful by inhalation and through the skin)
   - R43 (May cause sensitisation by skin contact)
   - R36/37/38 (Irritating to eyes, respiratory system and skin).

2. Human experience indicates that irritation, CNS depression and possible changes in liver and kidney function may follow occupational over-exposure (IPCS, 1993) inhalation being the presumed route of exposure.

3. No data on skin penetration.

6. In the absence of human data, the relevance of skin absorption as a route of exposure can be estimated from acute animal toxicity data. In this instance, a comparison of the $LD_{50\text{-dermal}}$ and $LD_{50\text{-inh.}}$ was made (IPCS, 1993):
   The acute $LD_{50\text{-dermal}}$ for 1,3-DCP in the rat is in the range 0.42-1.09 g/kg, with a median value of 1,009 mg/kg. The $LC_{50\text{-inh.}}$ for 1,3-DCP is in the range 3042-5403 mg/m^3, mean value 3,377 mg/m^3.

   The $LD_{50\text{-inh.}}$ (mg/kg) can be calculated from the $LC_{50\text{-inh.}}$ (using the formula given in Appendix A, Section 2.4 (c)):
   $LD_{50\text{-inh.}}$ = LC_{50} [mg/m^3] x ventilation rate [m^3/h] x 0.5 x exposure [h]/body weight Substituting $LC_{50\text{-inh.}}$ and other relevant values gives an $LD_{50\text{-inh.}}$ of 121.6 mg/kg.
   The mean measured $LD_{50\text{-dermal}}$ (1009 mg/kg) is < 10 x estimated $LD_{50\text{-inh.}}$ (121.6 mg/kg) indicating that skin absorption may be significant.

7. No. The substance cannot be excluded on the basis of low toxicity.

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	No	No	No	No

Reference

Environmental Health Criteria 146, 1993. 1,3-Dichloropropene, 1,2-dichloropropane and mixtures. IPCS, WHO, Geneva.

34. HEXAN-2-ONE (METHYL-n-BUTYLKETONE, MnBK*:* CAS 591-78-6)

1. Liquid: BP 127^{o}C and VP 0.5 kPa at 25^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R48/23 (Danger of serious effects to health by prolonged exposure through inhalation).

Neuropathological degeneration is the end-point of concern (DiVincenzo *et al*, 1978).

2. No circumstantial evidence from human skin exposure indicating that a Skin Notation may be required.

3. Experiments with 2 volunteers exposed to radio-labelled hexan-2-one indicated absorption rates of 4.8 or 8.0 μg/cm^2/min or 288 or 480 μg/cm^2/h respectively (DiVincenzo *et al*, 1978).

4. OEL is based on neuropathological effects.

5. This value can be compared directly with the outcome of the formula in Appendix A, Section 2.5, calculating 10% of the absorption during an 8-h exposure at the occupational limit of 20 mg/m^3. A retention factor of 75-92% has been reported in humans following inhalation exposure (DiVincenzo *et al*, 1978).

   The upper and lower CAV are 9.2μg/cm^2 (0.5×0.92×20) and 7.5 μg/cm^2 (0.5 x 0.75 x 20) respectively. Dermal absorption measurements of 288 - 480 μg/cm^2/h are > CAV (7.5 - 9.2).

TF Conclusion

A Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
Yes	Yes	No	Yes	Yes	Yes

Reference

DiVincenzo GD, Hamilton ML, Kaplan CJ, Krasavage WJ and O'Donoghue JL, 1978. Studies on the respiratory uptake, excretion and the skin absorption of methyl n-butyl ketone in humans and dogs. Toxicol. Appl. Pharmacol. 44, 593-604.

35. XYLENE (MIXTURE OF 3 ISOMERS: CAS 1330-20-7)

1. Liquid: BP 137-144 ^{o}C and VP 1.0 kPa at 20 ^{o}C

   EC "Classification and Labelling" Directive (67/548/EEC)
   Risk phrases:
   - R20/21 (Harmful by inhalation and by contact with skin)
   - R38 (Irritating to skin).

2. No circumstantial evidence from human skin exposure indicating that a Skin Notation may be required.

3. Information regarding dermal penetration in man is not reliable, since the available data were obtained using non-standardised procedures. For example penetration rates varied from 2 nmol/cm^2/h to 4.6 mg/cm^2/h (Dutkiewicz and Tyras, 1968; Engstrom *et al*, 1977; Lauwereys *et al* 1978 and Riihimäki, 1979).

6. $LD_{50\text{-dermal}}$ (rabbits) is 4,320 mg/kg (Hine and Zuidema,1970) and 12.182 mg/kg for m-xylene (Smyth *et al*, 1962). The $LD_{50\text{-inh.}}$ can be calculated from the $LC_{50\text{-inh.}}$ of 4,550 ppm (19.747 mg/m^3) (Proc Int Conf, Finland, 1975), which is the lowest value reported.
   $LD_{50\text{-inh.}}$ = 19.747 mg/m^3 x 0.0072m^3/h x 0.5 x 4h/0.4kg = 710 mg/kg

   The ratio of $LD_{50\text{-dermal}}$ / $LD_{50\text{-inh.}}$ ranges from 6-17.

   The very low dermal and inhalation toxicity lead to the conclusion that skin absorption is not important.

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	No	No	Yes	Yes	Yes

References

Dutkiewicz J and Tyras A, 1968. Skin absorption of toluene, styrene and xylene by man. Br. J. Ind. Med. 25, 243.

Engstrom K, Husman K and Riihimäki V, 1977. Percutaneous absorption of m-xylene in man. Int Arch Occup. Environ. Hlth. 39, 181-189.

Lauwereys RR *et al* ,1978. J. Occup. Med. 5, 143.

Hine CH and Zuidema HH, 1970. The toxicological properties of hydrocarbon solvents. Ind. Med. 39, 215-220.

Smyth HJ *et al* ,1962. J. Am. Ind. Hyg. Assoc. 23, 95.

Riihimäki, 1979. Percutaneous absorption of m-xylene from a mixture of m-xylene and isobutyl alcohol in man. Scand. J. Work Environ. Hlth. 5, 143-150.

Anon,1975. Proc Int Conf Univ Turku, Finland, 26.

36. DIPROPYLENE GLYCOL METHYL ETHER (DPGME: CAS 34590-94-8)

1. Colourless liquid: BP 188 ^{o}C and VP < 0.1 kPa at 20 ^{o}C.

   Not classified as dangerous to health according to Directive 67/548/EEC.
   Review of the available data (ECETOC 1995) confirms that DPGME does not require classification for systemic toxicity:
   $LD_{50\text{-oral}}$ > 2000 mg/kg
   $LD_{50\text{-dermal}}$ > 2000 mg/kg
   $LC_{50\text{-inhalation}}$ exceeds the limit of the achievable concentration.

   DPGME is:
   - not irritant to skin or eyes,
   - not a sensitiser,
   - not toxic to reproduction,
   - not toxic to the heamatopoietic system,
   - not genotoxic.

Comment

These characteristics indicate that DPGME has a very low toxicity. The capacity for skin penetration would otherwise probably have led to a skin notation. (Dugard *et al*, 1984).

TF Conclusion

No Skin Notation is recommended.

ECETOC	ACGIH	D	NL	S	UK
No	Yes	No	No	No	No

References

ECETOC, 1995. The toxicology of glycol ethers and its relevance to man. Technical Report No. 64.

Dugard PH, Walker M, Mawdsley and SJ, Scott RC, 1984. Absorption of some glycol ethers through human skin *in vitro*. Environ. Hlth. Persp. 57, 193-197.

APPENDIX D. 'SKIN NOTATION', DESCRIPTIONS IN THE REFERENCE COUNTRIES

American Conference of Government Industrial Hygienists (USA)

(reproduced with permission of the ACGIH)

"Skin" Notation

Listed substances followed by the designation "Skin" refer to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance. Vehicles present in solutions or mixtures can also significantly enhance potential skin absorption. It should be noted that while some materials are capable of causing irritation, dermatitis, and sensitization in workers, these properties are *not considered relevant* when assigning a skin notation. It should be noted, however, that the development of a dermatological condition can significantly affect the potential for dermal absorption.

While limited quantitative data currently exist with regard to skin absorption of gases, vapors, and liquids by workers, the Chemical Substances TLV Committee recommends that the integration of data from acute dermal studies and repeated dose dermal studies in animals and/or humans, along with the ability of the chemical to be absorbed, be used in deciding on the appropriateness of the skin notation. In general, available data which suggest that the potential for absorption via the hands/forearms during the workday could be significant, especially for chemicals with lower TLVs, could justify a skin notation. From acute animal toxicity data, materials having a relatively low dermal LD_{50} (1000 mg/kg of body weight or less) would be given a skin notation. Where repeated dermal application studies have shown significant systemic effects following treatment, a skin notation would be considered. When chemicals penetrate the skin easily (higher octanol-water partition coefficients) and where extrapolations of systemic effects from other routes of exposure suggest dermal absorption may be important in the expressed toxicity, a skin notation should be considered.

Substances having a skin notation and a low TLV may present special problems for operations involving high airborne concentrations of the material, particularly under conditions where significant areas of the skin are exposed for a long period of time. Under these conditions, special precautions to significantly reduce or preclude skin contact may be required.

Biological monitoring should be considered to determine the relative contribution of exposure via the dermal route to the total dose. The TLV/BEI Booklet contains a number of adopted biological exposure indices, which provide an additional tool when assessing the worker's total exposure to selected

materials. For additional information, refer to “Dermal Absorption” in the “Introduction to the Biological Exposure Indices”, 6th edition of the *Documentation of Threshold Limit Values and Biological Exposure Indices*, and to Leung and Paustenbach.

Use of the skin designation is intended to alert the reader that air sampling alone is insufficient to accurately quantify exposure and that measures to prevent significant cutaneous absorption may be required.

Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Germany)

(Abstract from List of MAK and BAT Values 1994, Deutsche Forschungsgemeinschaft, Document 30)

Cutaneous absorption

Certain substances can penetrate the epidermis easily; absorption of such substances through the skin can pose an incomparably larger danger of toxicity than their inhalation so that potentially fatal poisonings, frequently without warning symptoms, can result from cutaneous absorption of, e.g. aniline, nitrobenzene, ethylene glycol dinitrate phenols, certain pesticides, etc. Such substances are designated with an “H” in the relevant column in the list of MAK values. To avoid health risks when handling such substances, meticulous cleanliness of the skin, hair and clothing is imperative. The letter “H”, however, does not indicate a potential danger of skin irritation!

Dutch Export Committee on Occupational Standards (The Netherlands)

(Abstract from De Nationale MAC-lijst, 1995; Dept of Social Affairs and Employment, Publication P145. Translated from Dutch)

Skin absorption

Substances that may be absorbed relatively easily through the skin and as such can contribute substantially to the total internal exposure, are designated in the list with an “H”. For these substances adequate measures to prevent skin contact are required in addition to measures against inhalation. The Expert Committee applies the criteria formulated in ECETOC-document No. 31 when designating a skin notation.

Statute book of the Swedish National Board of Occupational Safety and Health (Ordinance AFS 1990:13) on Occupational Exposure Limit Values. (Sweden)

Absorption through the skin

Certain chemical substances can penetrate the skin, even when the skin is uninjured, and in this way be absorbed into the body. This applies particularly if the substances are present in solid form or as a liquid or as concentrated gas. The absorption from liquid (and also from concentrated gas) can be considerable. The prescribed limit value will provide adequate protection only on the condition that absorption through the skin cannot take place to such an extent that the total exposure is affected. Special measures are required to prevent absorption through the skin, if there is a risk of this.

Many substances can be injurious not only by absorption in the body but also by their direct effect on the skin and mucous membranes. Solvents degrease the skin, and thereby render it more vulnerable to the effects of both solvents themselves and other substances. Corrosive substances can cause particularly serious injuries to the eyes.

Substances that can easily be absorbed into the body also through the skin are identified in the Appendix.

Occupational exposure limits 1995 - Publication EH40/95 (United Kingdom)

Absorption through the skin

In general, for most substances, the main route of entry into the body is by inhalation and the exposure limits given in this booklet solely relate to exposure by this route. However, certain substances have the ability to penetrate the intact skin and become absorbed into the body, thus contributing to systemic toxicity; these substances are marked in the tables with an “Sk” notation. ACTS has agreed the following criteria for assigning this notation:

The “Sk” notation is assigned in cases where the available data or experience (or predictions made in the absence of actual data) suggest that exposure via the dermal route may make a substantial contribution to body burden (when compared to the contribution attributable to inhalation exposure at the OEL) and cause systemic effects, so that conclusions about exposure and health effects based solely on airborne concentration limits may be invalid.

Absorption through the skin can result from localised contamination, for example from a splash on the skin or clothing, or in certain cases from exposure to high atmospheric concentrations of vapour. This may result in a substantial body burden, so that serious effects may result with little or no warning.

Therefore it is necessary to take special precautions to prevent skin contact when handling these substances. Where the “Sk” notation has been assigned and the methods of use provide a potential exposure route via skin absorption these factors should be taken into account in determining the adequacy of the control measures. Further guidance is given on the adequate control of exposure by routes other than inhalation in the General COSHH Approved Code of Practice, in "The safe use of pesticides for non-agricultural purposes" and in "The safe use of pesticides on farms and holdings".

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Decision Scheme to Decide on a Skin Notation