ECETOC

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STRATEGY FOR ASSIGNING A "SKIN NOTATION"

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SECTION 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) (Appendix A) 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" (Appendix B). 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.

SECTION 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 [1]3000cm² = 0.3m²) confronted with a mean air velocity of 2km/h sweep a volume of 2000 x 0.3 x 8m³ per 8h shift. This amounts to 4,800m³ per shift which is so much greater than the corresponding inhaled volume (conventionally 10m³) 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.

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[1] In the calculation in Section 2.5, 2000cm² is taken for the surface of hands and forearms, excluding face and neck.

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 inhalational 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

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

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 200mg/kgbw and the dermal LD_{50} is at least 2,000mg/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 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 1h could amount to more than 10% of the amount that can be absorbed via the lungs on exposure to the OEL for 8h, *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 criterion 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 [a]2,000cm², that a volume of [b]10m³ is inhaled in 8 hours and that a fraction f (by default assumed to be [c]0.5) of the atmospheric contaminant is absorbed by the lungs, the [d]10% criterion corresponds to an absorption rate per hour (R) of

$$R = \frac{10^{b}\,[m^3] \times (OEL[mg/m^3]) \times f}{2000^{a}\,[cm^2] \times 10^{d}} = \frac{OEL \times f}{2000}\,\frac{[mg]}{[cm^2]}$$

Where

$$R > 0.5 \times f \times OEL\ \frac{\mu g}{cm^2}$$

or, using the default value ([c]0.5) for f, where

$$R > 0.25 \times OEL\ \frac{\mu g}{cm^2}$$

"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 2000cm² skin in 1h 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.

APPENDIX A: LISTS OF OCCUPATIONAL EXPOSURE LIMITS

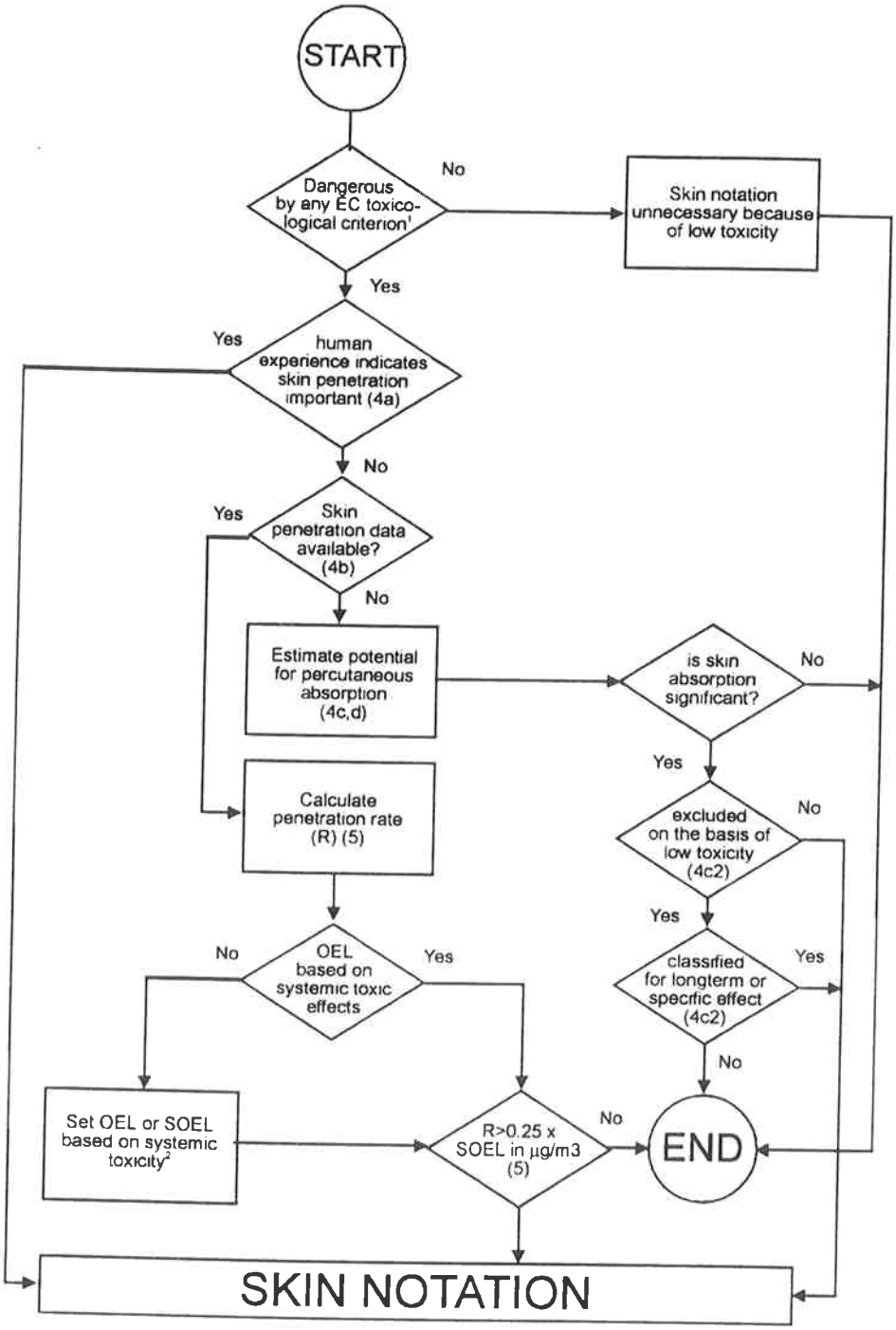
1. De Nationale MAC-lijst, Arbeidsinspectie P145, Directoraat van de Arbeid, Voorburg, The Netherlands.

2. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte, Deutsche Forschungsgemeinschaft, Mitteilung der Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe, VCH Verlagsgesellschaft, Weinheim, Germany.

3. Threshold Limit Values for chemical substances and physical agents and biological exposure indices, American Conference of Governmental Industrial Hygienists (ACGIH), 6500 Glenway Ave., Bldg. D7, Cincinnati, Ohio 45211-4438, USA.

4. Occupational Exposure Limits, Health and Safety Executive (HSE), Library and Information Services, Broad Lane, Sheffield S3 7HQ, UK.

APPENDIX B: DECISION TREE FOR "SKIN NOTATION"



1) Including non-acute specific effects.

2) SOEL = OEL purely based on systemic toxicity.

The figures in brackets, e.g. (4a), refer to subsections of Chapter 2.

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