# WES Review 2018

## *Criteria for assignment of a skin notation*

***Accessory document to Recommending health-based workplace exposure standards and notations***

*Australian workplace exposure standards and advisory notations*

Safe Work Australia (2018)

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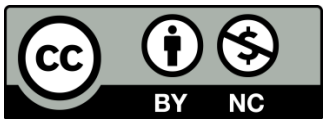


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# Glossary, abbreviations and acronyms

| Glossary | | | |
|---|---|---|---|
| **ACGIH®** | American Conference of Governmental Industrial Hygienists | **$K_{aq}$** | Permeation coefficient in the watery epidermal layer |
| **AIHA** | American Industrial Hygiene Association | **$K_p$ value** | Skin permeation coefficient |
| **AIOH** | Australian Institute of Occupational Hygienists | **$K_{pol}$** | Permeation coefficient in the protein fraction of the stratum corneum |
| **DECOS** | Dutch Expert Committee on Occupational Safety | **$K_{psc}$** | Permeation coefficient in the lipid fraction of the stratum corneum |
| **Dermal route** | Exposure via the skin, mucous membranes and eyes | **$LC_{50}$** | Concentration of a substance in air that kills 50% of animals during the observation period |
| **DFG** | German Research Foundation (Deutsche Forschungsgemeinschaft) | **$LD_{50}$** | Single dose of a substance that can be expected to cause death in 50 per cent of animals when administered by a given route of exposure |
| **ECETOC** | European Centre for Ecotoxicology and Toxicology of Chemicals | **NIOSH** | National Institute for Occupational Safety and Health |
| **GHS** | Globally Harmonized System of Classification and Labelling of Chemicals | **NOAEL** | No observed adverse effect level |
| **HCIS** | Hazardous Chemical Information System | **Occupational exposure limit** | Equivalent term to a workplace exposure standard |
| **HSE** | Health and Safety Executive | **OECD** | Organisation for Economic Co-operation and Development |
| ***In silico*** | Procedure performed via a computer | **PCBU** | Person who conducts a business or undertaking |
| ***In vitro*** | Procedure performed in a controlled environment outside of a living organism | **SCOEL** | Scientific Committee on Occupational Exposure Limits |
| ***In vivo*** | Procedure performed in a living organism | **SI ratio** | Skin/inhalation ratio |
| **IP** | Intraperitoneal | **WES** | Workplace exposure standard |
| **IPCS** | International Programme on Chemical Safety | **WHS** | Work Health and Safety |
| **IV** | Intravenous | | |

# Criteria for assigning a skin notation

This document outlines criteria for the assignment of a skin notation, an advisory notation to the workplace exposure standards.

## Background

Exposure standards represent airborne concentrations of chemical substances in the workers' breathing zone which, according to current knowledge, should neither cause adverse health effects or undue discomfort to workers (Safe Work Australia, 2013).

Under the model Work Health and Safety (WHS) laws, persons who conduct a business or undertaking (PCBUs) have a responsibility to ensure, so far as reasonably practicable, workers and other people are not exposed to health and safety risks arising from the business or undertaking (section 19 of the model WHS Act).

Additionally, under the model WHS laws, PCBUs have a responsibility to ensure that no person at the workplace is exposed to a substance or mixture in an airborne concentration that exceeds the exposure standard for the substance or mixture (regulation 49 of the model WHS Regulations). Therefore, in Australia, the exposure standards listed in the *Workplace Exposure Standards for Airborne Contaminants* are legally enforceable and duty holders must not exceed these standards.

Australia's workplace exposure standards are published with advisory notations associated with the hazardous chemical. These notations consist of:

- classification of carcinogenicity
- classification of sensitisation, and
- the potential for systemic effects due to skin absorption.

The notations are provided with the exposure standard for information only, so a PCBU and workers can take informed action to minimise exposure and risks.

Workplace exposure standard (WES) values are generally assigned to be protective of toxicity by the inhalation route. However, dermal exposure to some airborne chemicals may also significantly contribute to systemic effects associated with the chemical. Where significant exposure and toxicity may occur as a result of dermal absorption from airborne concentrations of the chemical, a skin notation will be assigned.

This notation will inform PCBUs and workers that maintaining airborne concentrations of the chemical at the workplace exposure standard may not be sufficiently protective as significant additional exposure may occur via the dermal route, including the skin, mucous membranes and eyes. PCBUs and workers can apply risk minimisation procedures as necessary; extra precautions to minimise total exposure, via both the inhalation and dermal routes may be warranted. This notation is used to help improve safety outcomes in the workplace.

While a 'skin' notation is assigned by most international agencies that determine workplace exposure standards, including the American Conference of Governmental Industrial Hygienists (ACGIH®), EU Scientific Committee on Occupational Exposure Limits (SCOEL), American Industrial Hygiene Association (AIHA), German Research Foundation (Deutsche Forschungsgemeinschaft; DFG) and the Health Council of the Netherlands, the criteria for assigning such a notation differ across these agencies (Lavoue et al., 2008; Nielsen and Grandiean, 2004; Sartorelli et al., 2007).

Several chemicals in the Australian WES list have an accompanying skin notation. These notations were generally assigned and adopted from the same source as the WES value, either ACGIH® or UK Health and Safety Executive (HSE). In 2004-2005, a public consultation paper was released discussing the inclusion of skin absorption notations adopted from the HSE for some chemicals. In response to this consultation paper, the

Australian Institute of Occupational Hygienists (AIOH) identified that there were no clear criteria for determining whether a 'skin' notation should be assigned to a chemical and recommended that clear criteria be developed.

## Aim

The aim of this document is to establish clear criteria for the assignment of a skin notation in Australia. These criteria will be generally consistent with those used by most international standard setting agencies.

## Criteria for skin notation assignment by other agencies

The principles underlying a skin notation for a chemical are generally similar across agencies:

- evidence of significant dermal absorption
- evidence or a suggestion of systemic toxicity by the dermal route, and
- for some agencies, the extent of dermal absorption at the workplace exposure standard is significant.

However, the specific criteria differ across agencies (see Table 1), ranging from purely qualitative criteria (e.g. DFG), to a more quantitative approach (e.g. US National Institute for Occupational Safety and Health [NIOSH]). Because of these differences in specific criteria, there is significant variability in the assignment of a skin notation for a chemical across different agencies (Nielsen and Grandjean, 2004).

**Table 1** Criteria for skin notation assignment by other agencies

| Criteria for skin notation assignment |
|---|
| **American Conference of Governmental Industrial Hygienists (ACGIH®, 2016)** |
| • Applied to chemicals where dermal application studies have shown absorption that could cause systemic effects following exposure.<br>• May accompany a sensitiser notation for substances that cause respiratory sensitisation following dermal exposure.<br>• Recommends integration of data from acute dermal studies and repeated-dose dermal studies in animals and humans, along with an ability of the chemical to be absorbed through the skin.<br>• $LD_{50}$ less than or equal to 1000 mg/kg/day by the dermal route.<br>• A skin notation is not applied to chemicals that cause dermal irritation or corrosive effects in the absence of systemic toxicity. |
| **European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1993)[a] / Health Council of the Netherlands** |

**Criteria for skin notation assignment**

- Considers physical form of substance.
- Potential for dermal absorption:
  - Human case reports of systemic effects following skin exposure
  - Direct measures of dermal absorption in human beings or animals using *in vivo* or *in vitro* models
  - Definitive relationship between toxic doses by the dermal route and toxic doses by other routes (if dermal $LD_{50}$ is less than 10 times the intravenous (IV), intraperitoneal (IP) or inhalation $LD_{50}$), and
  - Structure-activity relationship.
- Combination of toxicity and skin penetration.
- If the amount absorbed by both hands and forearms in 1 hour could amount to > 10% of the amount that can be absorbed via the lungs on exposure to the occupational exposure limit for 8 hours (provided exposure limit is set based on systemic effects).
- The decision tree for assigning a skin notation is shown in Appendix 1.
- Classification of a chemical as irritant or corrosive should not exclude a skin notation.

**German Research Foundation (DFG, 2014)**

- Skin notation can be assigned for systemic effects or respiratory sensitisation following dermal exposure.
- Criteria in order of decreasing significance:
  - If field or workplace studies indicate significant dermal absorption contributes to toxic effects
  - Dermal absorption has been demonstrated in animal studies and toxic effects observed (no definitive cut-off values or $LD_{50}$ value ratios indicated)
  - Evidence of dermal absorption in *in vitro* studies (no definitive cut-off values indicated), and
  - On the basis of data for analogous substances or calculations with mathematical models, dermal absorption may be expected.

**Scientific Committee on Occupational Exposure Limits (SCOEL, 2013)**

- 'Substantial contribution' to total body burden via the dermal route – established on a case-by-case basis but may in general be of the order of 10% or more of the uptake from the inhalation route at the workplace exposure standard value:
  - Determination of the extent of dermal absorption (from *in vitro* or *in vivo* studies; comparison of dermal and IV or IP $LD_{50}$ values)
  - Case reports of systemic effects following skin exposure in human subjects, and
  - Evidence of substantial variation in biological monitoring data in groups with similar inhalation exposure.
- Essentially similar to ECETOC but no hierarchy of effects – weight of evidence approach.
- A skin notation is not intended to give warning of direct effects on the skin such as corrosivity, irritation or sensitisation.

| Criteria for skin notation assignment |
| --- |
| **National Institute for Occupational Safety and Health (NIOSH)** |
| • Has three skin notations:<br>○ SK:SYS (systemic toxicity by the dermal route; similar to skin notation assignment by other agencies; applicable to current discussion),<br>○ SK:DIR (adverse health effects resulting in damage or destruction of skin localised at or near point of contact, e.g. corrosion or irritancy), and<br>○ SK:SEN (skin exposure to a chemical may cause or contribute to an immune response).<br>• SK:SYS assignment:<br>○ Evidence of adverse human health effects following dermal exposure<br>○ Evidence of dermal absorption (*in vivo* and *in vitro* tests) – critical cut-off point 10%<br>– if data are consistently higher than 10%, the chemical is considered to have a high potential for dermal absorption, and<br>– computational prediction of > 10% skin absorption based on physicochemical properties (e.g. molecular weight, solubility, pH).<br>○ **Acute toxicity – if $LD_{50}$ < 2000 mg/kg by the dermal route (**Globally Harmonized System of Classification and Labelling of Chemicals [**GHS**] **cut-off value)**<br>○ Repeat-dose toxicity (including reproductive and immunotoxicity studies) – if no observed adverse effect level (NOAEL) < 1000 mg/kg from dermal study and NOAEL is based on systemic effects<br>○ Evidence of carcinogenicity in organs and tissues excluding skin following dermal exposure (evidence of systemic absorption), and<br>○ If the skin/inhalation (SI) ratio is ≥ 0.1; SI ratio = dermal dose/inhalation dose at the occupational exposure limit |

[a] Largely developed based on the semi-quantitative approach taken by the Health Council of the Netherlands (Dutch Expert Committee on Occupational Safety; DECOS)

## Evidence of dermal absorption

### *In vivo* dermal absorption data

The most reliable means for determining if a hazardous chemical is absorbed through the skin is from human or animal data. If there is evidence of systemic toxicity by the dermal route or the chemical has been detected in the systemic circulation following dermal exposure, there is a clear indication that the chemical has been absorbed through the skin. Toxicity by the dermal route will be covered later in this document.

Dermal absorption is generally expressed as a percentage of the applied dose. As the skin of rats and rabbits is more permeable than that of humans (OECD, 2004a), dermal absorption data from these animal species provide conservative estimates of the extent of absorption via the skin in human subjects (OECD, 2011). The permeability of the skin from guinea pigs, pigs and monkeys is generally more similar to that of humans (OECD, 2004). The most reliable dermal absorption data are from well-conducted studies in human subjects.

Most agencies (ECETOC, the Health Council of the Netherlands, NIOSH, and SCOEL) consider a dermal absorption factor of greater than ten per cent as ‘significant’ dermal absorption (Table 1). This value corresponds to the low/high dermal absorption cut-off value in the OECD Guidance Notes (OECD, 2011). Some agencies (e.g. SCOEL) will assign a skin notation based solely on significant *in vivo* dermal absorption data.

### *In vitro* dermal absorption data

*In vitro* assays using skin samples from humans or animals have been developed to estimate the extent of dermal absorption (OECD, 2004b). Further details of these assays will not be discussed here but are covered in the relevant OECD guidance documents (OECD 2004b; 2004c; 2011).

The usual output from these assays could be a skin penetration rate, skin permeability coefficient ($K_p$ value) or a percentage of absorption that could provide an indication of the

expected dermal absorption in human subjects. As mentioned above, mouse, rat and rabbit skin is more permeable than human skin, and thus provide conservative estimates of the extent of human dermal absorption. The appropriateness of the skin from other animal species with respect to similarities with human skin, thereby affecting the predictive ability of the *in vitro* assay for skin absorption in human subjects, would need to be considered if using the data to assign a skin notation.

Dermal absorption in human subjects is likely to be overestimated from *in vitro* data using human or rat skin (OECD, 2011), but these data are considered conservative estimates. Given the potential technical errors in the conduct of these *in vitro* studies (OECD, 2004c), and the data likely overestimate the extent of dermal absorption in human subjects, it is considered inappropriate to assign a skin notation based solely on *in vitro* skin absorption data in the absence of any evidence of toxicity by the dermal route. Agencies use either the dermal absorption estimate or the penetration rate to determine if 'significant' absorption of a chemical via the dermal route will occur at airborne concentrations at the workplace exposure standard (see **Extent of dermal absorption at the workplace exposure standard**), but this should be considered in conjunction with any *in vivo* dermal toxicity data.

### *In silico* (computational) prediction of dermal absorption

It is generally accepted that the ability of a compound to penetrate the skin can be related to the physicochemical properties of the compound (e.g. molecular weight, solubility, pH) (OECD, 2011; IPCS, 2006). NIOSH uses a predictive algorithm (the revised Robinson model) to determine the skin permeation coefficient ($K_p$; expressed in cm/h) (NIOSH, 2009; Dotson et al., 2011). The revised Robinson model was considered the most reliable compared with other predictive models (Wilschut et al., 1995). This model uses the physicochemical properties of a chemical (molecular weight [MW] and the chemical's octanol-water partition coefficient [$K_{ow}$]) relevant to its transport in the stratum corneum, the outermost layer of the skin.

The following equations are used to calculate the skin permeation coefficient ($K_p$):

$$K_p = \frac{1}{\left[\left(\frac{1}{K_{psc} + K_{pol}}\right) + \left(\frac{1}{K_{aq}}\right)\right]}$$

where:

- $K_{psc}$ is the permeation coefficient in the lipid fraction of the stratum corneum
$$\log K_{psc} = -1.326 + 06097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$$

- $K_{pol}$ is the coefficient in the protein fraction of the stratum corneum, and
$$K_{pol} = 0.0001519 \times MW^{-0.5}$$

- $K_{aq}$ is the coefficient in the watery epidermal layer.
$$K_{aq} = 2.5 \times MW^{-0.5}$$

NIOSH has noted that there are limitations in the types of chemicals to which the models may apply based on the experimental data used to develop the model (NIOSH, 2009):

- chemicals for which experimental $K_p$ values are not readily available to be used in the development of the model as they are not readily absorbed through the skin (inorganic substances, ionised substances, very high molecular weight substances)
- chemicals that reach the systemic circulation by a means that is not part of the model (hydrophilic substances with a small molecular weight tend to penetrate hair follicles and sweat glands), and

- the model does not account for evaporation; $K_p$ values for highly volatile substances are likely to be overestimates.

NIOSH is the only agency that will assign a skin notation based solely on computational predictions of dermal absorption; however, this is only assigned in the absence of data that would suggest systemic effects following dermal exposure are unlikely.

## Evidence of toxicity by the dermal route

All of the agencies in Table 1 consider if there is any evidence of toxicity via the dermal route in human subjects or animal studies. However, there are some differences as to how these data are considered.

### Human case studies

All agencies in Table 1 assign a 'skin' notation based on reports from worker case studies where adverse effects following dermal exposure have been reported. For most agencies, this evidence alone is sufficient for assignment of a skin notation (see Appendix 1). There is no specific dermal exposure cut-off value and no clear criteria are provided by any agency as to what might be considered an adequately reported study. As the quality of reporting and adequacy of exposure assessments can be highly variable, reports citing the absence of adverse effects in human subjects following dermal exposure should not be used as a criterion to dismiss the possibility of a skin notation. However, positive findings in human subjects following dermal exposure strongly suggest the need for a skin notation for that particular chemical.

### Acute-dose toxicity studies in animals

The standard output of an acute dermal toxicity study is a $LD_{50}$ value, which will allow the substance to be classified in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). A $LD_{50}$ value is a single dose of a substance that can be expected to cause death in 50 per cent of animals when administered by a given route of exposure.

Aside from DFG, all agencies in Table 1 will consider assigning a skin notation based on a definitive dermal $LD_{50}$ value or a relative $LD_{50}$ value. NIOSH will consider assigning a skin notation if the dermal $LD_{50}$ value is < 2000 mg/kg, while ACGIH® uses ≤ 1000 mg/kg as the cut-off value. The latter cut-off value has also been supported in published literature (Kennedy et al., 1993; Nielsen and Grandjean, 2004).

The GHS hazard statements with their respective cut-off values for acute dermal toxicity are shown in Table 2. A dose of 2000 mg/kg is the limit dose used in acute dermal toxicity studies (OECD, 2017). As such, there are no chemicals in the Hazardous Chemical Information System (HCIS) database[1] with a H313 hazard statement (i.e. $LD_{50}$ value greater than 2000 mg/kg but less than or equal to 5000 mg/kg).

**Table 2** GHS hazard statements for acute dermal toxicity

| Hazard statement code | Description of Hazard Statement | Acute toxicity range |
|---|---|---|
| **H310** | Fatal in contact with skin | $0 < LD_{50} \leq 200$ mg/kg |
| **H311** | Toxic in contact with skin | $200 < LD_{50} \leq 1000$ mg/kg |
| **H312** | Harmful in contact with skin | $1000 < LD_{50} \leq 2000$ mg/kg |
| **H313** | May be harmful in contact with skin | $2000 < LD_{50} \leq 5000$ mg/kg |

[1] Database located on the Safe Work Australia website that provides information on chemicals that have been classified in accordance with the GHS.

A preliminary screen of chemicals on the Australian WES list revealed:

- For those chemicals with a H312 hazard statement (i.e. dermal $LD_{50}$ value between 1000 and 2000 mg/kg):
  - 77% have a skin notation from at least one agency[2]
  - 33% have a skin notation from all agencies that have a report available for that chemical
- For those chemicals with a H311 hazard statement (i.e. dermal $LD_{50}$ value between 200 and 1000 mg/kg)
  - 95% have a skin notation from at least one agency
  - 74% have a skin notation from all agencies that have a report available for that chemical

Based on this information, a 1000 mg/kg cut-off value is considered reasonable for assignment of a skin notation. This is not suggesting that for chemicals with dermal $LD_{50}$ values > 1000 mg/kg a skin notation is not warranted. If additional data are available to indicate a skin notation may be warranted, these data may be preferred in the place of a $LD_{50}$ value. A $LD_{50}$ is a lethal dose, with mortality considered as the only end point. Non-lethal toxicities by the dermal route may be observed following a single dose to animals, but these toxicities are not factored when determining a $LD_{50}$ value. Moreover, single dose toxicity studies do not take into account toxicities observed following repeated dosing (e.g. cumulative toxicity, bioaccumulation of the chemical) (Nielsen and Grandjean, 2004). A $LD_{50} \leq 1000$ mg/kg indicates definitive toxicity by the dermal route. Therefore, $LD_{50}$ values can only reasonably be used to rule in the need for a skin notation, but not specifically to rule out the need for such a notation.

A skin notation is warranted when the extent of dermal absorption is significant relative to the inhalation route and may contribute to adverse effects. Some agencies consider the acute dermal $LD_{50}$ value with the $LD_{50}$ value obtained by the intravenous (IV), intraperitoneal (IP) or inhalation routes (ECETOC, Health Council of the Netherlands and SCOEL). A comparison of the dermal $LD_{50}$ value with the IV or IP $LD_{50}$ value may give an indication of the extent of dermal absorption. A comparison of the dermal $LD_{50}$ value with the inhalation $LD_{50}$ value[3] would give an indication of the relative toxicity and relative extent of absorption by the two different exposure routes. ECETOC, Health Council of the Netherlands and SCOEL consider assigning a skin notation if the dermal $LD_{50}$ is less than ten times the IV, IP or inhalation $LD_{50}$ consistent with a threshold of greater than ten per cent dermal absorption for assignment of a skin notation.

## Repeat-dose toxicity studies in animals

While all agencies in Table 1 consider data from repeat-dose dermal toxicity studies in animals, only NIOSH uses a definitive cut-off level; if the no observed adverse effect level (NOAEL) is < 1000 mg/kg/day from the dermal toxicity study (general or reproductive toxicity) and the NOAEL is based on systemic effects, NIOSH will consider assigning a skin notation to this compound.

The limit dose for repeat-dose dermal toxicity studies is 1000 mg/kg/day (OECD, 1981a; 1981b). However, compared with occupational exposures, a dermal dose of 1000 mg/kg/day is extremely high and it may be a questionable cut-off value. There are two categories in the GHS classification scheme for specific target organ toxicity following repeated exposure. The criteria for these categories and their respective dermal (rat or rabbit) guidance value ranges are shown in Table 3. Only chemicals demonstrating

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[2] Agencies examined include ACGIH®, AIHA, DFG, Health Council of the Netherlands and SCOEL.

[3] The $LC_{50}$ value needs to be converted to an $LD_{50}$ value using this formula:

$$inhal\ LD_{50}(mg/kg/day) = \frac{LC_{50}(mg/m^3) \times\ ventilation\ rate\ \left(\frac{m^3}{h}\right) \times f \times exposure\ period\ (h)}{body\ weight\ (kg)}$$

where: $f$ represents the fraction absorbed by the inhalation route.
The ventilation rate and body weight are species-specific factors.

adverse effects at ≤ 200 mg/kg/day by the dermal route would be classified according to one of the two criteria listed in Table 3. This further supports the suggestion that a repeat-dose toxicity cut-off value of 1000 mg/kg/day is considered unreasonably high as a cut-off value for skin notation. The GHS cut-off ≤ 200 mg/kg/day is considered a more appropriate cut-off for a skin notation. This would be consistent with the ECETOC approach where chemicals that lack a health classification (similar to a GHS classification) should be exempt from a skin notation (ECETOC, 1998).

Evidence of toxicity in a repeat-dose dermal toxicity study (NOAEL ≤ 200 mg/kg/day) would over-ride a dermal $LD_{50}$ value > 1000 mg/kg/day observed in an acute dose toxicity study; the repeat-dose toxicity study considers a broader range of end points than an acute dose toxicity study (e.g. non-lethal toxicities, specific target organ toxicity, effects associated with cumulative exposure, potential accumulation).

**Table 3** GHS hazard categories for specific target organ toxicity following repeated dosing

| Category | Dermal guidance value range |
|---|---|
| **Category 1:**<br>Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. | ≤ 20 mg/kg/day |
| **Category 2:**<br>Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. | 20 < dose ≤ 200 mg/kg/day |

## Extent of dermal absorption at the workplace exposure standard

While some countries have assigned a skin notation based solely on the ability of a substance to be absorbed through the skin (e.g. Denmark, Norway, Sweden; from IPCS, 2006), dermal absorption alone does not indicate if this route of administration significantly contributes to potential adverse effects at the workplace exposure standard concentration. The contribution of dermal absorption to the overall total body burden may be higher at lower airborne concentrations (SCOEL, 2013). Therefore, of particular interest for assigning a skin notation is the extent of dermal absorption at the workplace exposure standard level.

Both NIOSH and ECETOC have developed mathematical formulae to determine if the extent of dermal absorption at the workplace exposure standard is significant (i.e. greater than 10%). These approaches are summarised in Table 4. Both approaches are only valid if the workplace exposure standard is derived based on systemic effects, and the systemic effects are similar or are expected to be similar by the dermal and inhalation routes. There are a number of differences between the two approaches:

- The ECETOC approach compares the extent of dermal uptake and the inhalation dose at the workplace exposure standard, whereas the NIOSH approach compares the overall diffusion of the chemical through the stratum corneum and into the blood capillaries.
- There are differences in default assumptions: extent of inhalation absorption, the size of the exposed dermal area and the duration of exposure.

Despite these differences, NIOSH compared the output from the two approaches and a similar result was obtained (NIOSH, 2009).

**Table 4** Approaches for comparing the dermal dose with the inhalation dose at the occupational exposure limit

| Agency | Approach |
|---|---|
| **ECETOC** | • Assumptions:<br>○ exposed area: hands and forearms (2000 $cm^2$) for 1 hour<br>○ 10 $m^3$ air respired in 8 hours, and<br>○ default inhalation absorption rate (if unknown) – 50% (in practice > 50% appears to be assumed by DECOS[a]).<br>• Uses a dermal penetration rate (in $mg/cm^2/h$).<br>• Equations:<br>$Dermal\ dose = penetration\ rate\ (mg/cm^2/h)\ \times 2000\ cm^2 \times 1\ h$<br>$Inhalational\ dose\ at\ WES = WES\ (mg/m^3)\ \times 10\ m^3\ \times f$<br>where $f$ = inhalation absorption factor.<br>• If $Dermal\ dose\ /\ Inhalational\ dose$ > 0.1, a skin notation is warranted. |
| **NIOSH** | • The $K_p$ value represents the overall diffusion of the chemical through the stratum corneum and into the blood capillaries. This value can be predicted computationally (see '*In silico* (computational) prediction of dermal absorption').<br>• Assumptions:<br>○ exposed area: palms (360 $cm^2$) for 8 hours<br>○ 10 $m^3$ air respired in 8 hours, and<br>○ default inhalation absorption rate (if unknown) – 75%.<br>• Equations:<br>$Dermal\ dose = K_p\ (cm/h) \times water\ solubility\ (mg/cm^3) \times 360\ cm^2 \times 8\ h$<br>$Inhalational\ dose\ at\ WES = WES\ (mg/m^3)\ \times 10\ m^3\ \times f$<br>where $f$ = inhalation absorption factor.<br>If $Dermal\ dose\ /\ Inhalational\ dose$ > 0.1, a skin notation is warranted. |

[a] Dutch Expert Committee on Occupational Safety; DECOS

## Proposed criteria for a skin notation in Australia

A skin notation will be assigned if there is:

- evidence of significant dermal absorption, and
- evidence or a suggestion of systemic toxicity by the dermal route, particularly at air concentrations close to the workplace exposure standard.

Based on the information in the previous section, the following are proposed as criteria to consider for the assignment of a skin notation:

| Criterion | Comments |
|---|---|
| **Reports of adverse systemic effects via the dermal route in worker case studies** | For worker case studies to be used for assigning a skin notation there must be clear evidence that adverse systemic effects were the result of at least some dermal exposure. |
| **Dermal $LD_{50}$ ≤ 1000 mg/kg** | Dermal $LD_{50}$ values > 1000 mg/kg may give a misleading indication as to whether a skin notation is warranted.<br>Only definitive $LD_{50}$ values will be used. |
| **Dermal $LD_{50}$ / inhalation $LD_{50}$ < 10** | The ratio of dermal $LD_{50}$ and inhalation $LD_{50}$ values will only be considered if the dermal $LD_{50}$ value is ≤ 1000 mg/kg.<br>The limit dose in an acute dermal toxicity study is 2000 mg/kg (OECD, 2017), and the maximum recommended concentration for aerosols in an acute inhalation toxicity study is 2000 $mg/m^3$ (OECD, 2009).<br>If a $LD_{50}$ value is greater than the maximum tested dose in an acute dose toxicity study, then a ratio will not be examined. |
| **Dermal repeat-dose NOAEL ≤ 200 mg/kg** | If the NOAEL is the maximum tested dose and the maximum tested dose is ≤ 200 mg/kg, the dermal NOAEL will not be considered when deciding if a skin notation is warranted. |
| ***In vivo* dermal absorption factor > 10%** | Only applicable if the WES value is derived based on systemic effects (rather than local findings such as irritancy). |
| **Estimated dermal exposure at the workplace exposure standard > 10%** | The estimated dermal exposure at the workplace exposure standard is determined using a known *in vitro* penetration rate or using an estimated permeability coefficient (determined with the NIOSH equation), and using the ECETOC equation with a default inhalation absorption factor of 75%.<br>Only applicable if the WES value is derived based on systemic effects. |

These criteria are generally consistent in principle with the semi-quantitative criteria used by SCOEL, DECOS, ECETOC and NIOSH, and the qualitative criteria used by DFG and ACGIH®.

In a weight of evidence analysis, not all criteria have equal weighting in determining whether a skin notation is warranted. The hierarchy of effects is covered in the next section.

### Hierarchy of effects

When data are inconsistent or limited, a weight of evidence approach will be used. Based on this evaluation, one of four recommendations is possible:

- a skin notation is not recommended
- insufficient data to assign a skin notation, and
- a skin notation is recommended.

These recommendations will also be considered in the context of whether the WES value is based on systemic or local effects.

Figure 1 illustrates the significance of each piece of evidence for assigning a skin notation. This hierarchy is generally similar to that used by ECETOC, NIOSH and DFG.

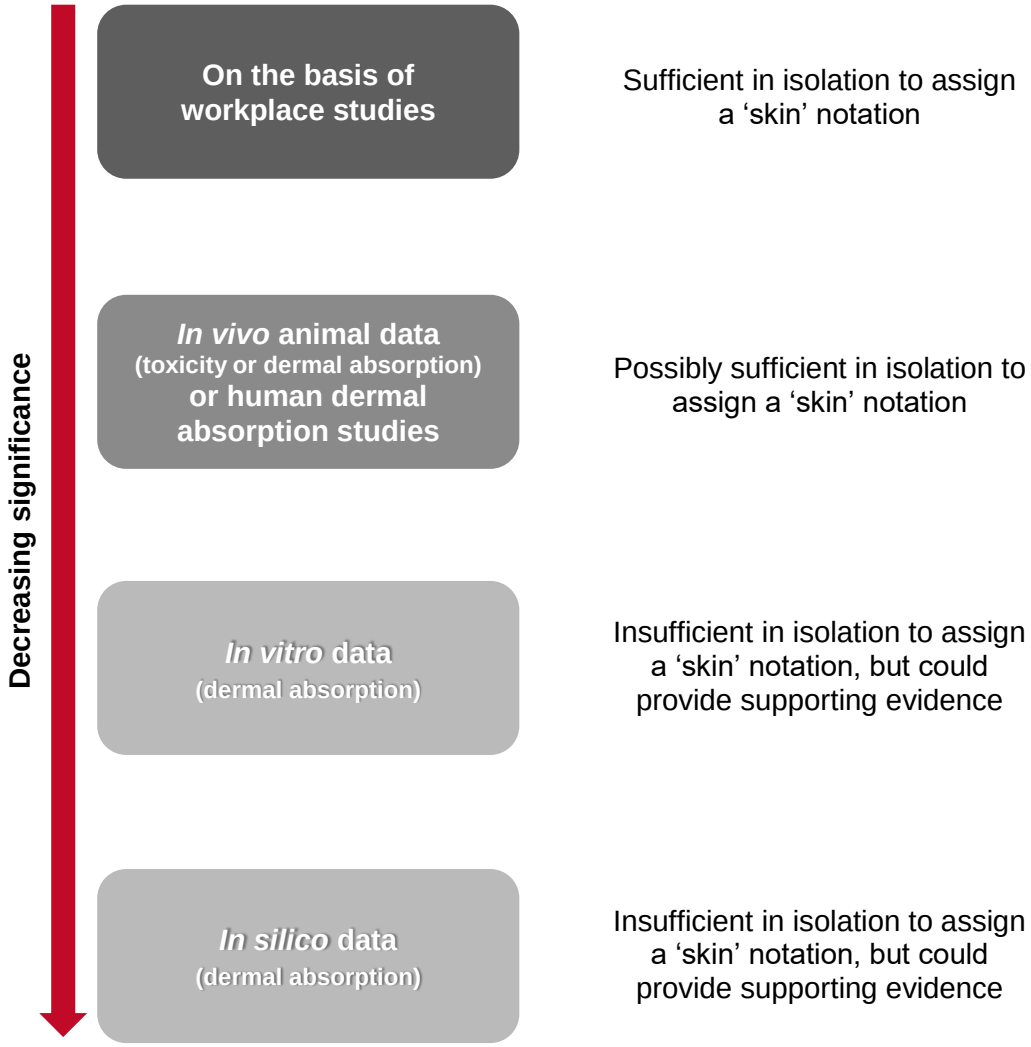


**Figure 1** Hierarchy of the weight of evidence for recommending a skin notation

The only data that are considered sufficient in isolation for the assignment of a skin notation is evidence of adverse systemic effects by the dermal route in human subjects. Data from animals may provide evidence a skin notation is warranted, depending on how close the data are to the relevant cut-off value.

In the absence of any *in vivo* data (dermal toxicity or *in vivo* dermal absorption data), a skin notation will not be assigned, particularly if the only available information is a predicted dermal absorption rate ('insufficient data to assign a skin notation').

The relative weight of each piece of information is shown in Table 5.

Based on the available data and the relevant weighting of the evidence, the evaluator will decide on a recommendation regarding assignment of a skin notation:

- If a skin notation is warranted, then a recommendation to assign a skin notation will be made.
- If a skin notation should be considered, the evaluator will decide, based on the totality of information, whether a skin notation will be recommended. The recommendation will be supported by a scientific argument. This argument may include a discussion of the quality of the available information.

- If there are insufficient data to assign a skin notation or a skin notation is not warranted, a skin notation will not be recommended.

**Table 5** Contribution of evidence to a skin notation

| Criterion | Result | Relevance |
|---|---|---|
| **Adverse findings in human case study** | Yes | A skin notation is warranted |
| | No | Provides no meaningful information |
| **Dermal $LD_{50}$ ≤ 1000 mg/kg** | Yes | Consider assigning a skin notation |
| | No | Provides no meaningful information |
| **Dermal $LD_{50}$ / inhalation $LD_{50}$ < 10** [a] | Yes | Consider assigning a skin notation |
| | No | A skin notation may not be warranted |
| **Dermal repeat-dose NOAEL ≤ 200 mg/kg** | Yes | Consider assigning a skin notation |
| | No | A skin notation may not be warranted |
| ***In vivo* dermal absorption factor > 10%** | Yes | Consider assigning a skin notation |
| | No | A skin notation may not be warranted |
| **Estimated dermal exposure at WES > 10%** [b] | Yes | Insufficient data to assign a skin notation |
| | No | A skin notation may not be warranted |

[a] Only relevant if dermal $LD_{50}$ value is ≤ 1000 mg/kg.
[b] This information is unnecessary if *in vivo* dermal absorption data are available.

## Local vs systemic effects

A skin notation will be assigned based on evidence of systemic effects by the dermal route. The criteria in the previous section Table 5have greater weighting if the WES value is derived based on systemic rather than local effects. If the data suggest a skin notation may be warranted according to the criteria and the workplace exposure standard is derived based on local effects, the relevance of the dermal absorption and toxicity data needs to be considered. If the NOAEL for systemic effects is close to the NOAEL for local effects, assignment of a skin notation will be considered. If there is a significant difference between the NOAEL for systemic effects and the NOAEL for local effects, a skin notation may not be assigned. These will be considered on a case-by-case basis.

For chemicals that are dermal irritants or are corrosive, good industrial practices and personal protective measures should prevent skin contact. It may seem redundant to assign a skin notation based on systemic effects to these compounds. However, irritant or corrosive warnings and skin notation warnings have different meanings and the provision of protective clothing against the irritant or corrosive activity may not always be true. When warranted to be protective for adverse systemic effects (based on the criteria in the previous section), a skin notation will be assigned to a dermal irritant or corrosive chemical. A skin notation will not be assigned to a dermal irritant or corrosive chemical in the absence of systemic toxicity.

# Other considerations

## Biological monitoring

For chemicals that have a skin notation, monitoring of airborne concentrations in line with the WES may not be protective for adverse systemic effects. To ascertain total systemic exposure, including by the dermal and inhalation routes, biological monitoring methods, if available, would be recommended. A comprehensive set of biological exposure standards has not been developed in Australia. However, advisory biological exposure limits are available domestically and internationally from ACGIH®, SCOEL and DFG.

## Effects of formulation and mixtures

Different formulations or chemical admixtures can influence the extent of dermal absorption. Some vehicles or solvents can act as carriers and when pretreated on the skin or mixed with a chemical can promote the transfer of the chemical into the skin. Skin notations assigned by most trusted bodies do not take into account the many possible formulations and combinations that include the chemical. As not all formulation combinations would have been considered with the available data to assign a skin notation, the absence of a skin notation does not imply that there is no risk of additional exposures by the dermal route. Precautions to minimise dermal exposure would still be warranted. If a skin notation is assigned, the extent of dermal absorption may vary considerably, depending on the formulation/mixture. Consideration should be given to the most appropriate type of glove depending on the mixture or formulation.

## Skin condition

There are several conditions that can affect the entry of chemicals and substances through the skin:

- some dermatological conditions
- damaged skin
- heat and humidity, and
- occluded skin, where the skin cannot perspire or respire.

Precautions to minimise dermal exposure may be warranted in these circumstances, even in the absence of a skin notation.

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## Appendix 1 — ECETOC decision tree for assigning a skin notation