The MAK Collection for Occupational Health and Safety

Criteria for designation with an “H”

MAK Value Documentation – Translation of the German version from 2014

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Keywords: skin absorption; skin penetration; dermal absorption; percutaneous absorption; exposure models; “H” designation; criteria; occupational exposure

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated criteria to designate substances with an "H" which can be absorbed via the skin in such amounts as to contribute significantly to systemic toxicity. Information on the uptake via the skin can be obtained from studies in humans, animals and from in vitro models preferably with human skin. Ideally, these data allow the calculation of a flux, i.e. the amount absorbed per cm^2 skin and hour. If these experimental studies are lacking, fluxes based on physicochemical data are calculated with three mathematical models for an aqueous saturated solution or a read-across to similar substances with a better database is used. For gaseous substances, the water solubility of the substance is calculated at a substance concentration in the gas phase that corresponds to the MAK value and the flux is modelled.
An exposure time of one hour and an exposed skin area of 2000 cm^2 which corresponds to the area of both hands and forearms is used as a practical exposure model for liquids. For gases, the exposure time is taken as 8 hours and the exposed skin area as 1.8 m^2.
With the obtained fluxes, the body burden is calculated and if it exceeds 25% of the chronic systemic NOAEL for workers, the substance is designated with an "H". If the substance is genotoxic and no systemic NOAEL could be deduced, a qualitative proof of uptake is enough for the designation with an "H".

Keywords

skin absorption; skin penetration; criteria; exposure models; evaluation; occupational exposure; maximum workplace concentration

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Criteria for designation with an "H"

Unlike for most toxicologically relevant properties, until recently there were no standardized test guidelines for the evaluation of absorption through the skin; this was particularly true for the dermal absorption of substances from the air (gas phase or aerosols). An OECD test guideline for in vitro and in vivo testing of absorption through the skin has only recently been developed (OECD 2004 a, b).

For most substances, investigation of the skin-penetrating property is not required by the regulations concerning the evaluation of toxicity. Exceptions are substances for which absorption through the skin is assumed to be a relevant route of exposure, such as agricultural pesticides, biocides and ingredients in cosmetic products. Therefore, for this aspect, relevant studies are not available for a large number of substances. In order nevertheless to be able to make reliable statements about the absorption of a substance through the skin, it is necessary to collect, evaluate and use all available information about the dermal absorption of this substance. Generally, the aim is to determine an absorption rate from available or derived data and assess percutaneous absorption taking into account practical conditions. It is then possible to decide whether to apply the "H" designation on the basis of the ratio between the amount absorbed and the parameters of systemic toxicity (for example the NOAEL (no observed adverse effect level)). Because of this quantitative approach, the "H" designation is a risk-based evaluation. Genotoxic carcinogens for which no systemic NOAEL can be established are designated with an "H" if skin penetration was detected qualitatively in studies or if percutaneous absorption is expected in analogy to structurally related substances. In these cases, the "H" designation is applied on a worst case and hazard basis.

1 Criteria for designation with an "H"

The types of studies and criteria the Commission uses to decide whether a substance should be designated with an "H" are described below. The various types of studies can be graded hierarchically with regard to their relevance for the derivation of the "H" designation for humans at the workplace; human studies have greater significance than animal studies, in vitro determinations and model calculations (Drexler 1998). The Commission evaluates the individual studies described in Section 1.1 to Section 1.3 with regard to their relevance and validity for the "H" designation. Model calculations are carried out on the basis of published algorithms as described in Section 1.4.

1.1 Human studies

Human studies are the most significant because they do not require interspecies extrapolation, which is a source of uncertainty. The various study concepts that may be used for this criterion are listed below.

Type of study	Evaluation criteria
a) immersion of a part of the body in the liquid substance and analysis of the exposure in human biological materials	comparison of the resulting body burden with the BAT value or NOAEL
b) application to the skin in a vehicle and analysis of the exposure in human biological materials (possibly also by determination in the vehicle after application)	calculation of the amount absorbed from the applied dose, the size of the exposed area and the exposure period, if possible; data in % of the amount applied are not very suitable because the results are dependent on the amount applied
c) exposure from the gas phase and analysis of the exposure in human biological materials	ratio of amount absorbed by inhalation to that absorbed dermally
d) case reports if symptoms of intoxication were observed and the exposure was not the result of an accident	case-by-case decision

1.2 Animal studies

Animal studies in vivo can demonstrate the processes of absorption, distribution and metabolism. Better absorption through the skin is generally expected in the commonly used species rat and rabbit because, for example, of the higher hair follicle density than in humans. However, this does not apply in every case (OEHHA 2000). The various study concepts that may be used to evaluate this criterion are listed below.

Type of study	Evaluation criteria
a) toxicokinetics/metabolism study: application to the skin in a vehicle, diluted or undiluted; analysis in biological materials	calculation of the amount absorbed/cm^2 from the applied dose, the size of the exposed area and the exposure period, if possible; data in % of the amount applied are not very suitable because the results are dependent on the amount applied
b) level of the dermal LD_{50}	dermal LD_{50} < 1000 mg/kg body weight can only be used if the substance is not corrosive or severely irritating because the epidermal barrier is otherwise destroyed; this does not correspond to the exposure conditions at the workplace
c) ratio of the oral/dermal LD_{50}	ratio of the oral to dermal LD_{50} may indicate good or poor absorption through the skin if oral absorption is known

d) repeated dermal application	comparison of the NOAEL/LOAEL with that from studies with other routes of exposure
e) absorption from the gas phase	from a) and e): evaluation of the ratio of dermal absorption of the gaseous substance/dermal absorption of the liquid substance

1.3 In vitro models (humans, animals)

In vitro models are suitable for determining absorption through the skin, and OECD test guidelines have been developed for conducting these. Studies in human skin should be given precedence for the reasons described under 1.2. The various types of studies that may be used for this criterion are listed below.

Type of study	Evaluation criteria
application to the skin in a vehicle, diluted or undiluted; evidence in the receptor phase and skin	calculation of the amount penetrated/cm^2 on the basis of the applied dose, the size of the exposed area and the exposure period, if possible; calculation of the steady-state flux; data in % of the amount applied are not very suitable because the results are dependent on the amount applied.

1.4 Mathematical models

If no experimental data are available, mathematical models may be used to calculate fluxes based on the physicochemical data log K_{OW}, molar mass and water solubility. For this calculation, the Commission evaluated and has been using the 3 models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) (Korinth et al. 2012).

The flux is calculated for a saturated aqueous solution or a solution with a concentration that is not irritating to the skin. The Fiserova-Bergerova model always yields the highest fluxes. The evaluation always takes the results of all 3 models into account as the prognostic reliability of each of the models alone is not considered to be adequate (Korinth et al. 2012). In cases of doubt, the highest calculated flux is used for the evaluation unless results from in vivo or in vitro studies with structurally related substances indicate a different conclusion.

1.5 Analogies

In the absence of other data that can be evaluated, an evaluation may be based on analogy using findings from structurally related substances with similar physicochemical properties that were investigated in more detail. Furthermore, analogies may be used to decide which result from the above-mentioned models is the most plausible. Conclusions drawn on the basis of analogy are always considered case-by-case.

1.6 Summary

Absorption through the skin may therefore be evaluated using a wide range of criteria and studies. This is to ensure that if substances comply with the evaluation criteria (Section 3), the "H" designation can nevertheless be given even in the case of insufficient data, which otherwise would not have been possible.

2 Exposure models

2.1 Liquid and solid substances

As the actual dermal exposure at the workplace is generally not known, assumptions about the type and duration of exposure have to be made when carrying out a risk-based evaluation of absorption through the skin. For this purpose, calculations are based on a 1-hour exposure of 2000 cm^2 skin (corresponding to the area of both hands and forearms), as proposed by ECETOC (1993). Exposure to a saturated aqueous solution is assumed when mathematical models are used for the calculation. Experimental study data are used according to how the studies were carried out and documented. However, studies with irritating or corrosive concentrations are not included in the evaluation because the purpose of the "H" designation is to provide protection against prolonged unnoticed exposure to non-irritating concentrations of a substance. If necessary and possible, data are converted to a non-irritating concentration.

2.2 Gases

In this case, the exposure scenario corresponds to 8-hour exposure of the total body surface. Although recent studies (Sacco et al. 2010; Tikuisis et al. 2001) determined an average body surface area of 1.91–2.03 m^2 for men and 1.71–1.73 m^2 for women, the body surface area is calculated using the standard body weight of 70 kg and respective body height of 170 cm (Reference Man ICRP 1975).

Based on whole-body scans, the following formula was established to assess the overall body surface area of men (Tikuisis et al. 2001):

$$\text{body surface area in } cm^2 = 128.1 \times (\text{body weight in kg})^{0.44} \times (\text{height in cm})^{0.6}$$

Accordingly, the body surface area of a man weighing 70 kg at a height of 170 cm is 1.8 m^2.

By means of Henry's constant, the water solubility of the substance is calculated at a substance concentration in the gas phase that corresponds to the MAK value. On this basis, the 3 models described by Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) are used to calculate the amount that is absorbed by a body surface area of 1.8 m^2 in 8 hours.

3 Evaluation criteria

A substance is generally given the "H" designation if the estimated amount that is absorbed through the skin is at least 25% of the long-term systemic NOAEL for humans. If necessary, this NOAEL has to be derived from animal studies as specified in the List of MAK and BAT Values.

The 25% value mentioned above is a convention. Lower values are probably below the measuring accuracy or in the normal range of variation of inhalation exposure at the workplace; a 50% and higher contribution of dermal absorption to the total exposure may, however, result in a relevant hazard.

The systemic NOAEL, should one be available, is the decisive reference value for designation with an "H", not the MAK value. This means that the systemic NOAEL has to be considered for substances with a MAK value established on the basis of irritation. Substances that do not have a MAK value because of a lack of irritation data may nevertheless be designated with an "H" if they comply with the above-mentioned evaluation criteria.

In the case of gases, the calculated amount absorbed through the skin is compared with the amount of substance absorbed by inhalation over an 8-hour period. The same evaluation criteria apply. If this does not result in the designation with an "H", this means in practice that absorption through the skin from the gas phase does not substantially contribute to the health risk only if the MAK value is observed (see Section VII of the List of MAK and BAT Values).

The same procedure applies also for genotoxic substances (germ cell mutagens or systemically genotoxic substances). Experimental evidence of penetration through the skin is sufficient for genotoxic substances for which there is no systemic MAK value, because in this case no safe exposure level can be given and dermal exposure increases the body burden. The induction of respiratory tract sensitization as a result of skin contact may be further qualitative evidence of absorption through the skin. Therefore, in this case, a risk-based evaluation is not made.

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