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THE SKIN NOTATION IN THE MAC LIST AND CLASSIFICATION OF DANGEROUS CHEMICALS

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Abstract
The European Union has published a list of dangerous chemicals, along with classification and labeling; in 1997 the list was adapted to the requirements of Polish regulations and has been continuously updated since then. We have decided to adopt data on dangerous chemicals classification in the list referring to their dermal absorption to assess whether the skin notation is required in the maximum admissible concentration (MAC) list. In Poland, the Group of Experts for Chemical Agents (GECA) decides on assigning the skin absorption notation (symbol Sk) when analyzing the literature data collected in order to prepare occupational exposure limits documentation. The LD_{50s} value serves as the main criterion for assigning the notation. The limit value of 1000 mg/kg has been set as the criterion for applying the skin notation. Documented results of animal and human research, which point to systemic effects resulting from dermal exposure and physicochemical characteristics enabling calculation of the dermal absorption rate may also be used as the basis for assigning the skin notation. Chemicals for which GECA recommended using the skin notation in the 2004 MAC list have been analyzed. It was concluded that information on the classification of chemicals in the list of dangerous chemicals is useful for assessing the skin absorption, but quantitative assessment of absorption rate compared to "safe" levels, using the available theoretical models, should also be attempted.

Key words:
Skin notation, Maximum admissible concentration, Classification

INTRODUCTION

The problem of deciding which chemicals are dangerous to human life or health due to their absorption through the skin in the occupational environments is still a matter of dispute. This issue has been discussed during toxicological conferences and seminars on industrial hygiene, and it has been also the subject of numerous scientific papers. The assigning of skin notation in the lists of maximum admissible occupational exposure levels has been discussed by various expert groups, including: EU Scientific Committee of Occupational Exposure Limit (SCOEL), German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, European Centre for Ecotoxicology and Toxicology of Chemicals, Dutch Expert Committee on Occupational Standards (DECOS), American Conference of Governmental Hygienists (ACGIH), Occupational Safety and Health Administration (OSHA), and the Group of Experts for Chemical Agents (GECA) in Poland. In the existing lists of hygiene standards prepared in various countries, the skin notation is given in the form of alphanumeric symbol, usually dependent on the concerned national language, e.g., Sk(in), S(kin), H(aut), H(uid), Sk(óra), etc. No consistent criteria for assigning the notation have been proposed, hence discrepancies could be observed in assigning the notation to the same chemicals in different countries. Literature data show that the accessibility of experimental data on the rate at which chemicals are absorbed through the skin is limited.

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Besides, when several reports specifying numeric data on skin absorption are available for the same chemical, the values may differ by 10 to 100 times. Therefore, it is not surprising that assigning the skin notation to individual chemicals differs between various expert groups.

ASSIGNING THE SKIN NOTATION TO CHEMICALS

The strategy for assigning the skin notation to chemicals is based on various quantitative and qualitative criteria. Those criteria have been described in detail by Nielsen and Grandjean [1] and Czerczak and Kupczewska [2]. The usual practice is to adopt the value of LD_{50s} (median lethal dose when the chemical is applied to the skin of an experimental animal) determined experimentally as the indication to provide the skin notation. Thus, two LD_{50s} values could be found in the literature: 2000 mg/kg [3] and 1000 mg/kg [4].

Skin absorption rate calculated from physicochemical characteristics of a concerned chemical in a suitable model is assumed to be the skin absorption index [5]. Skin absorption rate is calculated from the formula (eq. 1)

$$Fl = \frac{C_{sat}}{15}(0.38 + 0.153 \cdot P) \cdot e^{-0.016MW} \qquad (1)$$

where:

MW – molecular weight of chemical;

P – octanol/water partition coefficient;

C_{sat} – concentration of chemical in saturated aqueous solution.

Based on the integrated criteria, i.e. $LD_{50s} < 1000$ mg/kg, results from prolonged human and animal studies indicating the ability to be absorbed through the skin, physicochemical characteristics, which determine the absorption, e.g., high octanol/water partition coefficient, extrapolation of the systemic effects observed after the exposure by routes other than through the skin, ACGIH recommend the notation indicating that the chemical is absorbable through the skin. The American hygienists stress that the skin notation is not applicable to corrosives or irritants, which do not show any systemic activity [6].

The position of the German Commission has been expressed by Drexler [7] who says that the notation should be used "when the maximal allowable concentration (MAK) value for the substance is not sufficient to protect dermally exposed persons from adverse effects on their health". The German criterion fails to consider the relation between skin absorption on one hand, and hazard and exposure on the other, and is intended primarily to prevent from the irreversible effects [1]. Thus, if the dermal penetration is not manifested by health effect, the skin notation is not used. The consequences of using the skin notation in Germany have been clearly stated – a worker in contact with a chemical provided with the skin notation must be subjected to biological monitoring (BM). The advantage of applying BM is that it provides the quantitative assessment of the risk in a specific case, but in practice, validated methods for biological monitoring for many chemicals are not available.

The Dutch strategy is based on the quantitative assessment of absorption rate (R) as follows (eq. 2):

$$R = \frac{10^{b}(m^3) \cdot OEL(mg \cdot m^{-3}) \cdot f^{c}}{2000^{a}(cm^2)10^{d}} \qquad (2)$$

where:

the area of the hands and the forearms is $^{a}2000$ (cm^2), $^{b}10$ (cm^3) is inhaled in 8 h, a fraction (f) of $^{c}0.5$ of the atmospheric contaminants is absorbed by the lungs, at the $^{d}10\%$ criterion of the Dutch Expert Committee on Occupational Standards.

Thus, after substituting numeric values in the formula, we receive (eq. 3):

$$R[\text{in}\,\mu g/cm^2] = 0.25 \cdot OEL[mg \cdot m^{-3}] \qquad (3)$$

The skin notation is recommended whenever R (in $\mu g/cm^2$) $> 0.25 \cdot$ OEL (mg/m^3).

Thus, the Dutch Expert Committee on Occupational Standards assumes that the skin notation should be used whenever the quantity of chemical absorbed through the surface of the skin of the arms and forearms during 1 h is greater than 10% of the quantity absorbed by the lungs during 8-h exposure to the concentration of the chemical equal to the maximal occupational exposure limit [8].

The Swedish Group of Experts proposes to use dermal uptake index (D) that relates the dermal absorption rate (Pskin) to the respiratory uptake rate (Presp) via inhalation at occupational exposure level (OEL) according to the equation (4) [9]:

$$D = \frac{P_{skin}}{P_{resp}} \cdot k \qquad (4)$$

Both rates are calculated at steady-state and with fixed conditions (reflected by k) with respect to exposed skin area, pulmonary ventilation and relative respiratory uptake. Logarithmic transformation is performed to facilitate the interpretation and to account for the wide range in D values. The correction factor 8 is chosen to obtain a positive range of integer values for pD (eq. 5). It includes the constant k.

$$pD = \log_{10} D + 8 \qquad (5)$$

The authors conclude that when chemicals on various OEL lists are arranged according to their pD values, it becomes clear that the existing skin notations are not only inconsistent between institutions; they are also frequently inconsistent with the potential importance of dermal uptake.

The EU Scientific Committee of Occupational Exposure Limit is of the opinion that the skin notation should be used for those chemicals for which the available data show that the quantity of the concerned chemical absorbed through the skin is higher than 10% of the quantity of that chemical absorbed by respiration during 8-h exposure at the concentration equal to OEL [10]. The SCOEL experts recommend using *in vivo* and *in vitro* models to determine dermal absorption in humans and animals and stress at the same time that in many instances the absorption data are not available. The report also recommends comparing LD_{50s} value for dermal exposure with LD_{50s} value for intraperitoneal or intravenous exposures to obtain quantitative assessment of the absorption rate. Proofs of significant dermal absorption rates may be also obtained from human results, such as:

- case reports of systemic effects following skin exposure,
- substantial variation in biological monitoring data in groups with similar inhalation exposure,
- phenomena like subjective taste after "skin only" exposure.

In the absence of other data, an indication of likely skin penetration may be inferred from physicochemical data or structure/activity relationships.

The Polish Group of Experts for Chemical Agents decides on assigning the skin absorption notation (symbol Sk) when analyzing the literature data collected in order to prepare occupational exposure limits documentation. The LD_{50s} value serves as the main criterion for assigning the notation. The limit value of 1000 mg/kg has been set as the criterion for applying the skin notation. Documented results of animal and human research, which point to systemic effects resulting from dermal exposure and physicochemical characteristics enabling calculation of the dermal absorption rate may be also used as the basis for assigning the skin notation.

Aim

The aim of this work is to adopt data on dangerous chemicals classification in the list of dangerous chemicals to assess whether the skin notation is required in the maximum admissible concentration (MAC) list.

The European Union has published a list of dangerous chemicals along with classification and labeling [11]; in 1997 the list was adapted to the requirements of Polish regulations and has been continuously updated since then. The list has been published in the EU since 1967 and has been recently updated for the twenty-ninth time. It contains almost four thousand dangerous chemicals. The listed chemicals are classified by world-famous experts of the European Chemical Bureau (ECB), according to the developed and accepted classification criteria. Chemicals and preparations that, when absorbed through the skin in very small quantities, may cause death or acute/chronic health effects are classified as very toxic and are assigned the symbol "T+" in the list, accompanied by the phrase indicating the type of the hazard, "R27 Very toxic in contact with the skin" according to the following criterion: LD_{50s} dermal, rat or rabbit: ≤ 50 mg/kg.

Chemicals and preparations that, when absorbed through the skin in small quantities, may cause death or acute/chronic health effects are classified as toxic and are assigned the symbol "T" in the list, accompanied by the phrase indicating the type of the hazard, "R24 Toxic in contact with the skin" according to the following criterion:

LD_{50s} dermal, rat or rabbit: $50 < LD_{50s} \leq 400$ mg/kg.

Chemicals and preparations that, when absorbed through the skin, may cause death or acute/chronic health effects are classified as harmful and are assigned the symbol "Xn" in the list, accompanied by the phrase indicating the type of the hazard "R21 Harmful in contact with the skin" according to the following criterion:

$LD_{50s,}$ dermal, rat or rabbit : $400 < LD_{50s} \leq 2000$ mg/kg.

The authors have decided to adopt the data on dangerous chemicals classification in the list referring to their dermal absorption to assess whether the skin notation is required in the MAC list.

Method

Chemicals for which GECA recommended using the skin notation in the 2004 MAC list, have been analyzed. During that period, GECA proposed hygiene standards for 33 chemicals, for 13 of the analyzed chemicals, GECA recommended using the skin notation. It has been decided to assign three asterisks (***) to the chemicals classified as very toxic in contact with the skin, two asterisks (**) to the

Table 1. Chemicals for which GECA suggested the use of skin notation in 2004

Chemical name (CAS No.)	TWA (mg/m^3)	STEL (mg/m^3)	Basis for assigning skin notation	Category of dangerous chemicals as per list of dangerous chemicals
Chloroacetyl chloride (79-04-9)	0.28	0.6	Rat LD_{50s}: 662 mg/kg	**
Diethylamine (109-89-7)	15	30	Rat LD_{50s}: 630 mg/kg Rat LD_{50s}/rat 820 mg/kg	*
Ethyl acrylate (140-88-5)	20	40	Rabbit LD_{50s}: 500 µl/kg Systemic effects of dermal exposure	*
Methyl acrylate (96-33-3)	14	28	Rat LD_{50s}: 1300 mg/kg Rabbit LD_{50s}/rabbbit: 1243 mg/kg Systemic effects of dermal exposure	*
Bromomethane (74-83-9)	5	15	Systemic effects of dermal exposure Elevated concentration of bromomethane in blood plasma during occupational exposure	Irritating to skin
Xylene – all isomers (95-47-6; 108-38-3; 106-42-3; 1330-20-7)	100	Not established	Absorption rate Vapor: 0.6 $\mu g/cm^2/h$ Liquid: 0.113 $mg/cm^2/h$	*
Toluene (108-88-3)	100	200	Absorption rate Liquid: 0.69 $mg/cm^2/h$	Irritating to skin
4-Chlorophenol (106-48-9)	0.5	1.5	Rabbit LD_{50s}: 1000 mg/kg	*
2-(2-Methoxyethoxy) ethanol (111-77-3)	130	Not established	Absorption rate Liquid: 0.206 $mg/cm^2/h$	–
1-Chloro-4-nitrobenzene (100-00-5)	0.6	Not established	Absorption rate 0.016 $mg/cm^2/72$ h	**
2,2'-Iminodiethanol (111-42-2)	9	Not established	Systemic effects of dermal exposure 160 mg/kg/skn/mouse: hepatotoxic activity	Irritating to skin
2-Tolilamine (119-93-7)	3	Not established	Systemic effects of dermal exposure Hematuria – occupational exposure	–
1,2,3-Trichloropropane (CAS: 96-18-4)	14	Not established	Systemic effects of dermal exposure 250 mg/kg/rabbit	*

TWA – time weighted average; * Chemicals classified as harmful in contact with the skin;
STEL – short-term exposure limit; ** Chemicals classified as toxic in contact with the skin.

chemicals classified as toxic in contact with the skin, and one asterisk (*) to the chemicals classified as harmful in contact with the skin. Table 1 lists 13 chemicals, for which GECA suggested using the skin notation in 2004, together with TWA (time-weighted average concentration for a conventional 8-h workday) and STEL (short-term exposure limit) values and with the criteria for assigning the skin notation. Column 5 contains the number of asterisks assigned to the chemical according to the list of dangerous chemicals.

DISCUSSION

The 13 chemicals for which GECA had proposed the skin notation were analyzed. It should be noted that only for 4 of the 13 chemicals provided with the skin notation it was possible to propose biological exposure indices (BEI):

- xylene: 1.4 g methylhipuric acid/g creatinine
- toluene: 0.5 mg o-cresol/g creatinine
- 1-chloro-4-nitrobenzene
- 2-tolilamine: 2% MetHb.

Four chemicals, chloroacetyl chloride, diethylamine, ethyl acrylate and 4-chlorophenol were assigned the skin notation based on LD_{50s} values obtained from the literature data. The limit value for LD_{50s} at the level of 1000 mg/kg was used. These chemicals were classified, according to the list of dangerous chemicals, as harmful in contact with the skin (*), except for chloroacetyl chloride which is toxic in contact with the skin (**).

Nine chemicals were assigned the skin notation because of the systemic effects observed after dermal exposure. Data on the absorption rate were available for 4 of those chemicals. Three of the nine discussed chemicals, bromomethane, toluene and 2,2' iminodiethanol, were not included in the list of dangerous chemicals even as harmful in contact with the skin, but instead they were assigned the notation "R38 Irritating to skin". The following criterion was applied to classify a chemical as a skin irritant: "Substances and preparations that cause significant inflammation of the skin persisting for at least 24 h after an exposure period of up to 4 h determined on the rabbit according to the cutaneous irritation test method". Inflammation of the skin is significant if:

(a) the mean value of the scores for either erythema and eschar formation or edema formation, calculated over all the animals tested, is 2 or more; or

(b) following the test, using three animals, either erythema and eschar formation or edema formation equivalent to a mean value of 2 or more, calculated for each animal separately is observed in two or more animals.

Inflammation of the skin is also significant if it persists in at least two animals at the end of the observation time. Particular effects, e.g., hyperplasia, scaling, discoloration, fissures, scabs, and alopecia should be taken into account. Relevant data may also be available from non-acute animal studies. Chemicals and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact are also classified as irritating.

Two chemicals, 2-(2-methoxyethoxy)ethanol and 2-tolilamine, have not been classified in the list of dangerous substances for their harmful or irritating effect on the skin. It has been decided that the next step would comprise analyzing the rationality of providing the skin notation, based on the known criteria, to 3 chemicals assigned the notation and classified in the list of dangerous substances as irritating only (Table 2). The table specifies LD_{50s} values after the RTECS Data Base [12], while the information on assigning the skin notation are quoted after the Guide to Occupational Exposure Values [13], and the data on the experimental values are based on unpublished MAC documents prepared by GECA acting at the Nofer Institute of Occupational Medicine in Łódź, Poland. To calculate the rate (R), values of occupational exposure limits proposed by GECA in 2004 were used.

Only for toluene it is possible to compare the absorption rate determined experimentally with that calculated during exposure to chemical concentration equal to the 8-h OEL, assuming that the skin absorption is equal to 10% of lung absorption. The experimental value has been shown to be about 27.5 times higher than the "safe value". At the same time, the skin notation has been assigned by the quoted expert groups, except for OSHA. Thus, the classification of toluene in the list of dangerous chemicals merely as irritant in contact with the skin seems to require a revision.

Table 2. Chemicals assigned the skin notation and classified in the list of dangerous substances as irritating only

Chemical name	ACGIH Skin notation	OSHA Skin notation	MAK Skin notation	DUTCH/SCOEL R = 0.25 OEL (µg/cm²)	Physicochemical criterion (after Fiserova-Bergerova)	LD_{50s}	Absorption index – experimental data
Bromomethane	+	+	+	12.5	–	NA	–
Toluene	+	–	+	25	○	Rabbit: 12.4 g/kg	690 µg/cm²/h
2,2'-Iminodiethanol	+	–	+	2.25	●	Rabbit: 8340 mg/kg	–

+ Assigned skin notation; – No skin notation;
○ Significant dermal absorption potential; ● Potential for dermal toxicity (after Fiserova-Bergerova); NA – not available.

Table 3. Chemicals assigned the skin notation and not classified in the list of dangerous substances

Chemical name	ACGIH Skin notation	OSHA Skin notation	MAK Skin notation	DUTCH/SCOEL R = 0.25 OEL (µg/cm²)	Physicochemical criterion (after Fiserova-Bergerova)	LD_{50s}	Absorption rate – experimental data
2-(2-Methoxyethoxy) ethanol	?	?	?	32.5	–	2670 mg/kg	206 µg/cm²/h
2-Tolilamine	+	–	?	0.75	●	Rabbit: 3250 mg/kg	–

+ Assigned skin notation; – No skin notation;
● Potential for dermal toxicity (after Fiserova-Bergerova); ? Hygiene standard has not been set.

For 2,2'-iminodiethanol, experimental data is available indicating that its skin absorption in mice was about 60% of the applied dose, while in rats the corresponding value was about 16% of the dose [14]. Stott et al. [15] applied 2,2'-iminodiethanol to the skin of B6C3F1 mice at the daily dose of 160 mg/kg b.w. The same dose of 2,2'-iminodiethanol was applied intragastrically by gavage to other B6C3F1 mice. After cessation of the exposure, 2,2'-iminodiethanol concentration in the blood of the skin-exposed mice was 5 µg/g, while in the *per os*-exposed mice it was 7.7 µg/g. The 2,2'-iminodiethanol skin permeability was also assayed in an *in vitro* model. Skin pieces were collected from rats, mice, rabbits and humans, and aqueous 37% solution of ^{14}C-labeled 2,2'-iminodiethanol or 2,2'-iminodiethanol alone was applied. The human skin was the most efficient barrier to the aqueous solution, followed by rat, rabbit and mouse skin. Each time, 20 mg/cm² skin were applied for 6 h. The total dose of 2,2'-iminodiethanol absorbed through the skin from the aqueous solution, 0.23–6.68%, was higher than that when 2,2'-iminodiethanol alone was applied, 0.02–1.3% [16]. Considering those results, a review of the classification in the list of dangerous chemicals seems necessary also in this case.

Bromomethane is easily absorbable also through the skin, both in humans and experimental animals. Elevated levels of that chemical were detected in blood plasma of methyl bromide workers [17]. Quantitative data on the skin absorption are not available.

The remaining chemicals, 2-(2-methoxyethoxy)ethanol and 2-tolilamine, were tested in the same way, and they were not classified as harmful or irritating in contact with the skin (Table 3).

For 2-(2-methoxyethoxy)ethanol, it is possible to compare the calculated and experimental absorption rates when exposed to the chemical at levels equal to 8-h OEL, assuming that the dermal absorption is equal to 10% of pulmonary absorption. The experimental value has been shown to be 6.3 times higher than the "safe value". The absorption was 14 times slower than that for 2-methoxyethanol and comparable with that for 2-butoxyethanol [18] classified in the list as harmful in contact with the skin. Simultaneously, the available data show that the admissible exposure levels for that chemical in the United States and Germany have not been set. Hence, it seems necessary to revise the classification of 2-(2-methoxyethoxy)ethanol for its harmful dermal activity in the list of dangerous chemicals.

For 2-tolilamine in the conditions of occupational exposure, the skin is a very likely route of absorption. Numerical data from experiments are not available in the accessible literature. Fiserova-Bergerowa [5] has calculated the probable absorption rate of that chemical from its physicochemical characteristic and classified 2-tolilamine as harmful in contact with the skin. ACGIH has assigned the skin notation to 2-tolilamine in its list of admissible occupational exposure levels [13].

CONCLUSIONS

1) Information on the classification of chemicals in the list of dangerous chemicals is useful for assessing the skin absorption.

2) Current official list of dangerous chemicals comprises almost four thousand items, apparently a large number compared to several hundred in the list of hygiene standards of individual countries (479 in Poland). The information is easily accessible, e.g., from the European Chemical Bureau website, http://ecb.jrc.it

3) The information obtained from various sources should be revised using the most recent experimental data.

4) The quantitative assessment of absorption rate compared to "safe" levels, using available theoretical models, should be attempted.

5) Information contained in the list makes it possible to assess if a chemical mixture product is harmful, toxic or very toxic through the skin, using the conventional calculation method, from the contents of dangerous components, and e.g., their limit concentrations, this possibility seems to be of particular practical value.

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