

Comment Number	Comment	Response (Action required)
1-1	<p>Is the rationale and framework presented within the CIB scientifically valid? I agree the old skin notation system has significant limitations, and a new, more informative, comprehensive, and scientifically based skin notation system is long overdue. Exposure to workplace chemicals may cause occupational skin diseases, such as contact or allergic dermatitis, which are the most commonly reported non-fatal occupational illnesses. Data show that skin diseases account for 15.6% in 2004 and 16.5% in 2005, the largest percentage among those for other occupational illnesses. Despite the high incidence rate, skin exposure to various chemicals is not well characterized, and health effects and mechanisms are not well understood. Exposure methodologies are not well developed and standardized, which limits efforts to prevent these skin-exposure-related diseases. However, in recent years, skin exposures and assessment methodologies—and their potential health risks—have received more attention, more research, and better understanding. This improves our knowledge and allows the development of a new and more informative skin notation system that will benefit employers and employees, and it will promote hazard communications and efforts to prevent skin diseases and disorders.</p>	No action required.
1-2	<p>Is the rationale and framework presented within the CIB scientifically valid? I think the proposed new skin notation (system) is more comprehensive, more informative, more scientifically based and more updated. The framework in the new skin notation assignment method is (1) based on standardized literature review on current knowledge and therefore up to date, (2) more comprehensive including different types of potential risks and chemical reaction mechanisms and therefore more informative, (3) more scientifically sound and valid by reviewing the literature including both animal and human data and both potential health risk and physiochemical properties.</p>	No action required.
1-3	<p>Are the skin notation classifications appropriate? As described above, the classification is more inclusive and informative than the original skin notation. It distinguishes among systemic toxic effect, local direct contact effect, and sensitization effect. In the type of systemic effects, it signifies the most serious effects—the acute toxicity (fatal versus non fatal); and in the type of direct contact, it distinguishes simple irritation versus corrosion. It adds the sensitization category, which is good for protecting those susceptible workers. The use of combined symbols allows the expression of multiple effects to be noted and is appropriate to me.</p>	No action required.

Comment Number	Comment	Response (Action required)
1-4	Are the conclusions that form the basis of the recommendations appropriate? Appropriate	No action required.
1-5	For the symbols and effect categories, the only thing I was thinking of is how to denote the potential chronic/long-term and carcinogenic effects. Do we need another symbol (category), say CAN or CAR, for skin carcinogens (carcinogenic effects)? I would suggest so.	No action required.
1-6	If data are not conclusive on potential health effects, I would suggest not using any of the symbols because the symbol is there to alert; if there nothing to be concerned about, why alert? So if there is no data, or the data is inconclusive, no assignment is made. A special symbol in this case may cause confusion to people (try to figure out the proper meaning of it).	No action required.
1-7	On Executive Summary, Page viii, Line 18, add "s" to "indicate."	No action required.
1-8	Specify how often the notations are to be updated and what chemicals are included.	No action required.
1-9	A skin notation is not to be assigned based on mathematical modeling only; Specify the rationale for selecting chemicals to assign the skin notation.	No action required.
1-10	Since the notations are intended to harmonize with those by the international organizations, it is important to obtain the feedback from the international safety and health community, particularly from those in the Europe where skin exposure research has been more extensively conducted.	No action required.

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Skin notation is assigned in many countries for a wide range of chemicals. There is little evidence of any consistency in the approach adopted, either within or between countries. It is therefore an important development that NIOSH have produced a sound scientific basis for assigning skin notation. In addition, the introduction of a more elaborate skin notation has the potential to improve the clarity and utility of the information communicated. I support the NIOSH proposal for assigning skin notation for chemicals.

2-1

No additional action required

(Are the proposed classes of skin notations appropriate?) It is proposed to assign skin notation for systemic (SYS), direct (DIR), and sensitizing (SEN) effects. Substances that may be lethal following acute dermal exposures are designated with the systemic sub-notation (FATAL). Irritants and corrosive chemicals are indicated by the direct effects sub-notations (IRR) and (COR), respectively. These notations cover the main adverse health effects that may arise from skin exposure to chemicals. They therefore seem an appropriate set of classes for the skin notation.

2-2

No additional action required

(Are the proposed classes of skin notations appropriate?) My main concern with the proposal is in relation to the intended user base, which is not clearly defined in the present document. Mention is made of the NIOSH Pocket Guide to Chemical Hazards, which I understand is aimed at providing a "concise source of general industrial hygiene information for workers, employers, and occupational health professionals." The information in the Guide is quite technical and I think more suited to use by health and safety professionals rather than workers or employers.

2-3

The target audience is OSH professionals, researchers, and others with a scientific background. This document is not intended to be a non-technical document used by workers. Upon publication of this document, the new skin notation assignments will be added to the *Pocket Guide* and a topic page will be developed which will provide an overview of the document. No additional action required.

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(Are the proposed classes of skin notations appropriate?) The proposals for the skin notation sit well with the other information in the Pocket Guide. However, I note that there is already information in the Guide about entry routes into the body and target organs, both including skin. The assignment of skin notation and these other pieces of information in the Guide will need to be done with care. The totality of information may be open to some misinterpretation, e.g. if a chemical as assigned SK-SEN but did not have skin as a target organ.

2-4

The information within the *Pocket Guide* will be harmonized when the new skin notations are included. The reviewers comments will be taken into great consideration when adding the skin notations to the *Pocket Guide* and all other NIOSH publications. No additional action required.

(Are the proposed classes of skin notations appropriate?) The simple assignment of skin notation was open to misinterpretation, while this more complex notation may be too difficult for the non-technical user to fully understand.

2-5

See response to Comment 2-3.

(Are the proposed criteria for assigning each type of skin notation appropriate?) I believe that the approach adopted to assign skin notation are appropriate. The reliance on a broad range of in vivo, in vitro and modeling data will ensure that the assignments are based on the best available evidence. As noted above the assignment needs to be coordinated with the other information in the NIOSH Pocket Guide.

2-6

No additional action required

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(Is the proposed assignment of multiple skin notations useful for protecting workers from dermal hazards?) I believe this is an important step forward and I am sure that it will help protect workers from dermal hazards. My two main reservations are points that are recognized in the document: first that this is a designation of hazard rather than risk and second that it is only for the pure chemical and not the mixtures that are likely to be found in articles and preparations used in the workplace.

2-7

The issues of the skin notations 1) as indicators of potential hazards versus indicating quantitative risk and 2) applying strictly to neat compounds are addressed in Chapter 2.0 and Appendix G.1, respectively. No additional action required.

(Is the proposed assignment of multiple skin notations useful for protecting workers from dermal hazards?) In my opinion it is necessary for occupational hygiene practice to move beyond the management of dermal exposure on the basis of hazard and to provide tools to facilitate risk-based management strategies. For example, a relatively volatile agent assigned a skin notation is, in my opinion, unlikely to be systemically absorbed via the skin unless the worker has some fairly extreme exposure – e.g. immersion of part of their body in the liquid. However, with a hazard-based warning skin notation the users may be drawn towards the use of chemical protective clothing to protect a negligible risk. Currently we do not have good tools to make assessments of the risk from dermal exposure and this should be a priority for the future.

2-8

No additional action required

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(Is the proposed assignment of multiple skin notations useful for protecting workers from dermal hazards?) Substances in mixtures may behave differently from the pure chemical. It is impossible for a regulator to properly deal with the very large number of mixtures on the market. The link between the proposed skin notation and the Globally Harmonized System (GHS) for labeling chemicals will hopefully ensure that there is correspondence between the skin notation and labeling of chemicals in the marketplace.

2-9

No additional action required

(Should the SEN notation apply strictly to allergic contact dermatitis or is it appropriate to assign the SEN notation for other immune-mediate responses, such as respiratory sensitization, airway hyperactivity and mucosal inflammation, associated with dermal exposure to a compound?) Yes, I think it is appropriate to have a relatively wide definition of the potential sensitization hazard from skin exposure to chemicals. As far as the worker is concerned it is the fact that an adverse effect occurs as a consequence of dermal exposure rather than the final target organ for that effect. The authors make a good argument for the inclusion of respiratory sensitization from dermal exposure and I believe that this could be one of the more important developments from the changes in skin notation. Certainly in the UK there is some reluctance to recognize that skin contact with some chemicals may be a cause of respiratory sensitization. In my opinion this may be part of the reason why in the UK we have not seen the reduction in occupational asthma following the introduction of strict risk management measures for respiratory exposure to isocyanates.

2-10

The authors state within Section 2.4 that the SEN assignment will be assigned for health effects beyond allergic contact dermatitis (ACD); a few NIOSH internal reviewers indicated that the SEN should be strictly used to denote the potential of ACD. This reviewer's comment supports the assignment of the SEN for immune-mediated effects beyond ACD including respiratory sensitization, airway hyperactivity and mucosal inflammation. Based on this comments and other provided by external reviewers, SEN will be used to denote immune-mediated effects beyond ACD. Based on comment provide by other reviewers, additional information have been included throughout the document to clarify the assignment of the SEN for effects beyond ACD. No additional action required.

Comment Number	Comment	Response (Action required)
2-11	<p>Does the proposed harmonization scheme found in Appendix G.2 link the new NIOSH skin notations and the GHS assignments sufficiently? I am not an expert in the GHS but from what I have read in the document I am reassured that the proposed approach to assigning skin notation is consistent with GHS.</p>	<p>No additional action required</p>
2-12	<p>Should additional information be included within document? If so, what? The document should discuss how the new assignment will fit with the information already in the NIOSH Pocket Guide on target organs and exposure route.</p>	<p>We have indicated within the revised CIB that the new skin notations will be included within the Pocket Guide and other NIOSH documents. No additional action taken.</p>
2-13	<p>(Do the data cited support the objectives of the document?) I believe that the document provides a logical approach to assigning skin notation and is supported by appropriate scientific arguments. I could not find any explicit statement of the objectives of the document, but if it is to "promote the identification and control of dermal exposures to hazardous agents and conditions in the workplace" then I am certain that this document will have an important impact.</p>	<p>The purposes of this document can be found in the first paragraph of Chapter 2.0. The goals are to 1) to ensure that the assigned skin notations reflect the contemporary state of scientific knowledge, 2) to provide transparency behind the assignment process, 3) to communicate the hazards of dermal chemical exposures, and 4) to meet the needs of health professionals, employers and other interested parties in protecting workers from chemical contact with the skin. No additional action required.</p>
2-14	<p>(Are the conclusions appropriate in light of the current understanding of the toxicological data?) Yes, I consider that the conclusions that the authors have arrived at are appropriate in the light of the current toxicological data.</p>	<p>No additional action required.</p>

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2-15

On page 8 it is said "Protocols for testing chemicals developed by the Organization for Economic Cooperation and Development (OECD) and Registration, Evaluation, Authorization and Restriction of Chemical (REACH)." However, REACH is a European Union regulation rather than an organization. The relevant organization in Europe would probably be ECVAM (<http://ecvam.jrc.it/>) or another EU institution.

This comment has been noted and appropriate changes have been made.

No additional action required

Comment Number	Comment	Response (Action required)
7-1	Are proposed classes of skin notations appropriate? Yes	No action required.
7-2	Are proposed criteria for skin notation appropriate? Yes	No action required.
7-3	Multiple skin notations useful? Yes	No action required.
7-4	Should SEN be assigned for effects beyond ACD? Yes, very important to include sensitizing effects for respiratory sensitization associated with dermal exposure.	Please see Comment 2-10; No additional action required
7-5	Propose harmonization scheme? Seems reasonable.	No action required.

Comment Number	Comment	Response (Action required)
7-6	<p>What is the time frame for SYS (FATAL)?</p>	<p>This skin notation has been included within the CIB to provide a warning that a chemical is highly or extremely toxic and may be potentially lethal or life-threatening following skin exposures. It is intended to reflect an acute exposure to a chemical that may cause death or extreme systemic toxic effects following contact of the skin with a chemical. In regards to human exposures, no time frame for death has been included because of published case studies of individuals receiving a single exposure to a chemical dying anywhere from 20 minutes (i.e., 2,4-dichlorophenol) to 6 months (i.e., methyl mercury) after exposure. Inclusion of a time frame would limit the data used to assign the (FATAL) notation and potentially result in the notation not being assigned, which would endanger workers. In regards to animal data, established in vivo protocols [e.g., OECD guideline 402, United States Environmental Protection Agency (U.S.EPA) guideline OPPTS 870.1200 (Complete references can be obtained from Appendix A-pp. 21)]</p>
7-7	<p>Will you mention approximate dose for SYS (FATAL)?</p>	<p>Please see Appendix A.1.2; The dose of 200 mg/kg body weight has been selected at the critical numeric cutoff value for the assignment of the (FATAL) notation. This value corresponds with the criteria established by GHS for the assignment of the equivalent GHS hazard ranking. No additional action required.</p>
7-8	<p>Might be helpful to add notation for carcinogenicity, such as SK: DIR (CARC) vs. SK: SYS (CARC).</p>	<p>Please see Comment 1-5; No additional action required</p>

Comment Number	Comment	Response (Action required)
7-9	Would be helpful to further define SK: SENS (type I, type IV, etc), as it will indicate the kinds of reactions that workers might have, e.g. anaphylaxis is a risk for type I sensitization, but not for type IV.	Further defilement within the CIB is not needed because the support for the assignment of the SEN or other notation will be included within the Skin notation Profile; this includes the type of immunological reaction for which the SEN notation. No additional action required.
7-10	What about SK: SENS without dermatitis? For example, isocyanates can sensitize through the skin, yet a true contact dermatitis (vs. irritant or defatting) is rare.	When systemic sensitizing effects occur following dermal exposure and ACD does not occur, the SEN would be assigned if sufficient quality data are identified that supports its assignment. Additional information has been included in Section 2.4 to clarify this point. No additional action required.
7-11	Should SK: SENS include a SYS notation? This gets to the issue of anaphylaxis or severe systemic reaction.	Please see Comment 5-4; No additional action required.
7-12	Page 85, Table D.2.—some of these attributions don't look right. For example: i. Methyl isocyanate is 0 SENS, but is a sensitizer; ii. Dimethyl sulfate is 1 SENS, but I can find no information that demonstrates that it causes sensitization. There is information, however, indicating that systemic exposures, if high enough, can be fatal. [SK: SYS (FATAL)]. iii. This suggests that this table requires extensive review of the literature, and probably comments from experts.	NIOSH reviewed this issue and determined that a typographical error had occurred during the development of Table D.2. These chemicals had previously been identified correctly in regard to their potential to act as a sensitizer, in addition to the other hazard categories evaluated in the hierarchal ranking scheme. The table has been updated and the two chemicals identified by the reviewer have been replaced to ensure that additional errors associated with them are not included within the CIB.
7-13	Data cited supportive? Yes, but some areas need more work (see above).	No action required.
7-14	Conclusions appropriate? In general, yes. The document is very thought	No action required.

Comment Number	Comment	Response (Action required)
8-1	<p>(Are proposed classes of skin notations appropriate?) Yes. But would revise definition of "Sen."</p> <p>(Are proposed criteria for skin notation appropriate?) Yes. For Sen would clarify that sensitization can be documented by antigen specific immune responses other than patch testing. This is already implied /stated in some places, would just make more explicit. Ex - page 19 - line 7. (e.g. patch testing or antigen-specific immune responses such as antibody responses or lymphocyte proliferation.)</p>	<p>Based on additional comments from this reviewer, supplemental information has been included throughout the document (See Section 2.4) that is intended to clarify the effects that can receive the SEN notation. In addition, the SEN definition has been updated. No additional action required.</p>
8-2	<p>(Is the proposed assignment of multiple skin notations useful?) Yes.</p> <p>(Should the SEN notation apply strictly to ACD or is it appropriate to assign the SEN notation for other immune-mediated responses, such as respiratory sensitization, airway hyperactivity and mucosal inflammation, associated with dermal exposure to compound?) Yes appropriate to use for other immune-mediated responses. However terminology needs editing. Skin exposure or any exposure causes systemic sensitization. Sensitization is systemic condition (immune cells circulate). The immune / allergic response can occur at local sites (eg airways, lung, skin) following re-exposure (elicitation) at that site. Would avoid "respiratory sensitization" or wording that suggests that skin exposure causes asthma or diseases at distant sites. Skin exposure causes systemic sensitization that can contribute to subsequent development asthma following airway exposure. Skin or respiratory in front of sensitization usually refers to route of sensitization - via skin or respiratory track. To avoid confusion I try to separate the "site" from word "sensitization" since sensitization is systemic.</p>	<p>An additional statement has been included within Section 2-4 to address this comment and to clarify the assignment of the SEN notation. No additional action required.</p>
8-3	<p>(Is the proposed harmonization GHS scheme OK?) Yes.</p>	<p>No action required</p>
8-4	<p>(Is the proposed harmonization GHS scheme OK?) Yes.</p>	<p>The reviewer's comments have been taken into consideration and the appropriate changes have been made to Section 2.4: SEN to clarify the assignment of the SEN notation. Please also see other comments 8-1, 8-2, 8-4, 8-6, etc.</p>
8-5	<p>(Is the proposed harmonization GHS scheme OK?) Yes.</p>	<p>No action required</p>

Comment Number	Comment	Response (Action required)
8-6	<p>[Additional information ? (or less information)] Would minimize mechanistic discussion - eg Type I, Type IV. Current terminology is primarily IgE-mediated or cell mediated immune response. Since immunology quickly gets complicated, easy be "out-of-date" - less said probably the better.</p>	<p>This comment has been taken into consideration and language associated with this in Section 2.4: SEN has been rewritten to be more generic. Immune mediated effects are referred to as immediate and delayed instead of Type 1 and Type IV. No additional action required.</p>
8-7	<p>[Additional information ? (or less information)] Table E1 - page 68 - would add terms such as allergen, atopy, rhinitis, sinusitis, lung diseases (asthma, hypersensitivity pneumonitis, chronic beryllium disease etc), IgE, IgG, T cells, sensitization, etc. List is very complete for skin - less so for lung / allergy / asthma / immune responses terms.</p>	<p>Additional terms have been added to the list in Table E.1. No additional action taken.</p>
8-8	<p>[Additional information ? (or less information)] P 85 Table D2 - missing some key chemicals would rank in top 30 - but OK. Suspect that's because started with prior list 142 chemicals - and as noted list is only first 30 - NIOSH will get to others. E.g. Several key diisocyanates missing - MDI, HDI. Also anhydrides.</p>	<p>The list is merely an example and is populated with chemicals currently found within the Pocket Guide and have been assigned the skin notation [skin]. Chemicals beyond this group will eventually be reviewed and receive skin notations based on the information presented in Appendix D. No additional action taken.</p>
8-9	<p>[Additional information ? (or less information)] Terminology - as above some terms / definitions "sensitization" "sensitizing effects" "respiratory sensitization" need some edits to be more accurate immunologically.</p>	<p>See Comments 8-1, 8-2, 8-4 and 8-6. No additional action required.</p>

Comment Number	Comment	Response (Action required)
8-10	[Additional information ? (or less information)] "Dermal" refers to one layer of the skin - the dermis, which is below the epidermis. More accurate would be use of "skin" or "cutaneous" as in "skin exposure" or "cutaneous exposure".	The reviewer is correct about the use of terms "skin" and "cutaneous" in place of dermal, but the term "dermal" has become common vernacular and is after used in place of "skin" and cutaneous. For example, NIOSH refers to the NORA skin cross sector as the Dermal Cross Sector Program. To address this issue, "cutaneous," "percutaneous," and "dermal" have been added to the glossary with a definition indicating that the terms refers to the skin. A footnote has been added to Chapter 1 (first sentence) indicating that the terms are interchanged within the CIB with the skin where appropriate. Also, editing has harmonized the language and use of these terms to minimize confusion.
8-11	Additional info - quite complete.	No action required
8-12	Yes data cited OK.	No action required
8-13	(Are the conclusions of the document appropriate?) Yes.	No action required
8-14	Document overall very well done - and important contribution.	No action required
8-15	Remove sensitizing effects from glossary and include sensitization	Sensitizing effects have been removed and entry for sensitization included in the Glossary; change noted throughout document. No additional action required.
8-16	Replace the word "dermal" with skin	The term "dermal" has been replaced in many sections of the document with the term "skin"; additionally a glossary entry has been included to indicate that the following terms refer to the skin: "cutaneous", "dermal", "dermal contact", and "percutaneous". No additional action required.