Comment Number	Comment	Response (Action required)
3-1	I agree that the skin notation concept needs additional clarification to describe the type of skin effect and distinguish between local effects and systemic effects. As you know, other organizations also use the approach of adding a skin notation for systemic toxicity that occurs from dermal absorption of a material. Would it be possible to harmonize the NIOSH system with the other organizations, such as ACGIH and GHS? As a "customer" of various classification schemes, it is increasingly difficult to prepare appropriate safety and handling information with multiple classification schemes.	The new NIOSH skin notations have been harmonized with the GHS classification system. Appendix G.2 and Table G.2 provide an overview of the harmonization scheme. ACGIH assigns skin notations to chemicals that are dermal absorbed and/or identified as sensitizers. The new NIOSH skin notation provides supplemental information that exceeds the information provided by ACGIH. Adapting the ACGIH scheme would limit the application of the new NIOSH skin notations. No additional action required.
3-2	While I completely understand the need to differentiate between the varieties of skin and systemic effects encountered from dermal exposure the workplace, the detailed scheme described in CIB Strategy document is complex and may be more difficult for "customers" of the classification to apply.	Please see comment 2-3. No additional action required.
3-3	Also, there is an additional category of skin irritants that should be recognized, such as items that cause mechanical irritation (e.g. fiberglass, wool, silica, etc). This type of irritation is distinct from a chemical irritation or sensitization response, but deserves mention since because it often results in painful and/or visible dermal changes.	Within the strategy document, irritants are generically divided into two broad categories: (1) ICD (non-immune), and (2) ACD (immune mediated). Friction irritation is a form of ICD and would warrant the assignment of the DIR notation (if supported by data). Because other forms of ICD (e.g. acute ICD, chronic ICD, delayed acute ICD, acneiform ICD) are not singled out in this document, we have chosen not to single out friction. We agree with the reviewer that it is a true hazard and should be assessed as part of the skin notation strategy. No action taken.

Comment Number	Comment	Response (Action required)
4-1	Dow believes that employers and employees will benefit from an improved skin notation system that provides more specific and useful information about the specific risks from skin exposure. This system will correct some deficiencies in the current *NIOSH Pocket Guide* and provide useful information for the anticipation of health hazard risks and appropriate protective measures for workers, albeit with an additional level of complexity.	No action required.
4-2	The proposed classes of skin notations are appropriate for hazard awareness and communication, and appear to be clearer for workers, as well as OEHS professionals, when for a clear determination of effect from dermal exposure can be made. However, it is not clear what the notation would be if the studies are inconclusive or if there is inadequate data to put a specific notation on a substance. Clearly, if a chemical has been evaluated and does not warrant notations, the ~~**SK**~~ notation is appropriate versus a full compliment complement of notations when deemed appropriate.	See opening discussion in Chapter 2.0. Additional notations have been included to indicate when insufficient data exist to assign other notations and when a chemical has not been evaluated. No additional action required.

Comment Number	Comment	Response (Action required)
4-3	To assure the credibility of the notation used, care should be taken to make sure that the determination of "sufficient data" for a skin notation is robust and provides real likelihood of a skin effect in humans. Although the criteria are stated in the proposed strategy, there is room for interpretation and judgment in a "weight of evidence" methodology, particularly if the "scientific data" used for assigning skin notation are based on "mathematical modeling and predictive algorithms." Although the document seems to address this, there could be an overly conservative interpretation of certain data (e.g., quantitative structure-activity relationship (QSAR), dermal absorption, physical and chemical properties) that might not demonstrate adverse effects using experimental data. For example, in Dow's experience, initial investigations using three of the most prominent QSAR programs for dermal sensitization have about 60% accuracy against previous human and animal test results. Although the document suggests a combination of absorption estimates with a positive QSAR might result in a skin notation, discussion with Scott Dotson during the public hearing indicated otherwise. This at least reinforces the need for clear description of the criteria and methodology. These decisions are neither simple, nor black-and-white, and the process and criteria for such decisions need to include toxicologists and dermal experts when further clarification is needed. There needs to be consensus regarding the interpretation of such data, as well as the process for doing so. Again, using a QSAR example, programs typically provide results with reliability or domain estimates. These confidence estimates should be recognized, but the literature is replete with many investigators providing 'definitive' interpretations under unreliable circumstances. Dow recommends that NIOSH include a summary of how it will utilize a QSAR approach to lend insight into whether a notation applies by analogy and indicate the degree to which QSAR outcomes can "drive" the notation.	The issue of the use of mathematical modeling and predictive algorithms such as QSAR, DEREK, SI RATIO has been addressed in Section 2.1. This section has been included to clarify that computational techniques (i.e. mathematical modeling and predictive algorithm) can not serve as the sole basis of a skin notation assignment, but is intended to serve as support when the human and animal data is deemed to be limited (Appendix E). As the science behind these models improve and become more accurate, NIOSH may decide to put more weight behind the models and use them as the sole basis of a skin notation assignment.

Comment Number	Comment	Response (Action required)
4-4	If the calculations and decisions are overly conservative when data appear somewhat limited, then the result would be that far too many chemicals would be given the SK notation. This will result in a skin notation for many chemicals with little or no actual risk, while the same notation will be used for chemicals which that are truly dangerous, diluting the value of the skin notation. The dilemma with an ""overwarning"" situation such as this that employers and workers can tune out and ignore the risk when it seems everything is labeled as equally hazardous. This situation is exemplified by California's Proposition 65, leading one author to state, ""It can be postulated that by failing to focus on the known ris factors associated with specific health effects (e.g., cancer) in humans, [California's] Proposition 65 has diminished the ability and effectiveness of public health efforts to address those known risks.""[1]	The goal of the new skin notations is to alert workers and employers to the hazards of dermal contact with candidate chemicals. Their assignment is based on (1) the identification of an adverse health effect or increased risk of an adverse health effect associated with dermal exposures and (2) the framework outlined within the CIB. We acknowledge the reviewer's comment and agree that making the notations. To ensure that the skin notations are not too conservative, the mathematical models and predictive algorithms, which represent the greatest area of uncertainty, will not serve as the sole basis of a skin notation assignment (please see Comment 4-3). Additionally, Appendix E contains a paradigm for qualitatively ranking the assembled data set to ensure that a minimal level of quality data is available to make a skin notation assignment. No

Comment Number	Comment	Response (Action required)
4-5	Left unstated in NIOSH's scheme is clear indication of what should be done when the studies are inconclusive or if there are inadequate data or QSAR correlations to confirm or refute systemic toxicity, and yet various parameters (e.g., octanol-water partition) indicate that dermal absorption is likely. Dow believes that there should be some indication of the ""unknown" status of dermal absorption in the resulting NIOSH notation. Would there be a scenario proposed whereby a substance in this situation would not have any indication? Or rather, would NIOSH perhaps put an asterisk and a footnote regarding the expected absorption but lack of definitive data? Dow considers the failure to address this situation clearly as a key gap in an otherwise complete and detailed classification scheme.	For all chemicals evaluated via the strategy outlined in this CIB, a Skin notation profile will be developed and contain the support documentation for the assignment or lack of assignment of skin notations (see Appendix F). In addition, new skin notations have been added to the strategy document to indicate that insufficient data exist to assign skin notations and that a chemical has not been evaluated for dermal hazards. These skin notations will be integrated into the *Pocket Guide* and other NIOSH documents. No additional action taken.

Comment Number	Comment	Response (Action required)
4-6	The proposal indicates that the strategy for assigning skin notations has been developed to correspond with the classification strategy adopted in the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). This is commendable and it is recommended that both the strategy and the actual skin notation results match the GHS classifications. Many manufacturers sell their products globally, and it is likely that NIOSH's skin notation scheme will not be recognized worldwide. It would create problems to have different skin notations in different countries for the same chemical, if the organizations interpret data differently. It would be useful to know specifically how NIOSH plans to apply the skin notation classification of GHS. Dow strongly recommends that NIOSH provide a table (perhaps in an appendix) that compares and contrasts the scientific criteria for skin notations to clearly communicate the similarities and highlight any differences in classification in both systems.	This information was already included within Appendix G.2, which includes a table that compares the NIOSH guidelines with the GHS scheme. No additional action taken.
4-7	For those entities (such as manufacturers or distributors of substances) that must develop Material Safety Data Sheets (MSDSs), consideration must be given to the financial and resource impacts of updating these skin notations for materials with RELs if reported on their MSDSs. Dow suggests that NIOSH take the steps below to minimize the practical MSDS creation impacts:	See Comments 4-7-a through 4-7-d. No additional action required.

Comment Number	Comment	Response (Action required)
		These issues have been taken into consideration and input from stakeholders (e.g. Society of Chemical Hazard Communication) associated with MSDSs has been included in the development of the skin notations. No additional action required.
4-7-a	Consider the symbols and the space to report them on an MSDS or in a table. At a minimum, the format for ""Notations"" and the space allocated to them will need to be altered. Select only characters which that any word processor, database or internet Internet program can use, as some automated systems do not currently have the capability to utilize complex symbols beyond character strikeouts (use **~~SK~~** instead of **X**). At a later date, if the GHS and resulting MSDS structure are adopted in the United StatesS, additional graphic capabilities may be available at that time.	
4-7-b	Consider contacting the Society of Chemical Hazard Communication (SCHC) regarding their its OSHA Alliance Program on GHS and MSDSs to ensure they have consideredthere is consideration of an expanded Section 8 inclusion of skin notations.	See Comment 4-7-a
4-7-c	Because these skin notations are new and more complex, provide a concise sentence or definition for MSDS preparers to include as brief footnoted explanations of the NIOSH skin notations just below the RELs in Section 8 of the MSDSs, particularly where they deviate from the traditional ""Skin" notations.	This information was already included within the Abbreviations section. No additional action required.

Comment Number	Comment	Response (Action required)
		This document underwent its second stakeholder and public review in October 2008. The original review occurred in Spring 2004. In both cases, NIOSH requested that all interested parties review and make comment on this document. We feel that the document has undergone sufficient review and has been vetted sufficiently. No additional action taken.
4-8	NIOSH's proposed skin notation process could be leveraged globally, for instance, for inclusion in the European REACH Derived No Effect Levels (DNELs) for workers by the route of dermal exposure, and could potentially be adopted by other OEL-setting bodies. In the interest of applying the proposed skin notation scheme more broadly so that there are not multiple '"skin notation' notation" schemes potentially based on different criteria, Dow would suggest requesting technical reviews from the ACGIH TLV® Committee and the AIHA WEEL Committee requesting a harmonized approach to setting and communicating skin notations.	

Comment Number	Comment	Response (Action required)
5-1	Development of a new approach to assigning skin notations to hazardous substances is long overdue. Under the current system, reflected in OSHA's listing of permissible exposure limits (29 CFR 1910.1000, Table Z-1) and the Threshold Limit Values (TLVs) of the American Conference of Governmental Industrial Hygienists (ACGIH), substances are assigned a "Skin" notation where there is evidence that dermal exposure can contribute significantly to overall exposure via dermal absorption. Substances that exhibit direct dermal toxicity or sensitization are not assigned a "Skin" notation absent evidence of significant dermal absorption. (However, the ACGIH does assign a "SEN" notation to substances that cause dermal or respiratory sensitization through dermal exposure.) It is also the case that the basis for the existing system is not well understood by practitioners since because it omits consideration of direct dermal toxicity, and it is potentially confusing. Although the existing approach of assigning skin notations is useful to evaluate the need for personal protective clothing where there is potential for dermal exposure in the workplace, we believe the proposed NIOSH approach represents is a substantial improvement of the current system that will provide occupational health professionals with better hazard information on which to base their risk assessment and risk management decisions. Adoption of the proposed NIOSH approach should make clear to users that appropriate PPE may be necessary where employees are at risk of experiencing direct dermal toxicity even where evidence does not suggest that dermal exposure is likely to increase overall dose or body burden.	No action required.
5-2	The proposed classes of skin notations appropriately distinguish between direct dermal toxicity, systemic toxicity associated with dermal absorption, and skin or respiratory sensitization associated with dermal contact. In particular, we agree that the SK-SEN notation should be used where there is sufficient evidence that dermal contact causes either allergic contact dermatitis or sensitization of the respiratory system or mucous membranes. This is consistent with the approach taken by the ACGIH for assigning "SEN" notations that are accompanied by a "Skin" notation (see, for example, page 76 of the 2008 ACGIH TLV and BEI booklet). Restricting use of the SK-SEN notation only to where there is evidence of allergic contact dermatitis might lead to confusion where there is a disparity between the NIOSH and ACGIH skin designations.	Please see comment 2-10. No additional action required.

Comment Number	Comment	Response (Action required)
5-3	In general, the proposed NIOSH approach is consistent with the hazard determination approach taken in the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Both approaches rely on the same kinds of scientific evidence and use similar default LD50 values for assigning hazard statements/skin notations. However, classification of hazards associated with dermal contact of chemicals under both the proposed NIOSH system and the GHS necessarily rely on the use of professional judgment to evaluate and weigh evidence and make a hazard determination. For this reason, NIOSH-assigned skin notations may, in some specific instances, differ from hazard statements seen on labels and material safety data sheets prepared in accordance with the GHS, simply reflecting differences in scientific judgment. To ensure that users of the GHS and NIOSH systems understand this, it would be helpful for NIOSH to discuss a bit in Appendix G.2 how such apparent discrepancies might arise. The only area where it appears that NIOSH may have deviated from the GHS classification criteria to the NIOSH Skin Notation was in lines 7-11 on page 79 (Appendix F). NIOSH used the numerical cutoff value of 1000 mg/kg for repeated-dose dermal toxicity data. The GHS guidance value used to classify a chemical as a Target Organ–Single Exposure Category 1 is 1000 mg/kg. However, the data NIOSH cited was repeated dose data so the corresponding GHS guidance value for Specific Target Organ–Repeat Exposure Category 1 would be 20 mg/kg. However, NIOSH's conclusion with respect to the hazard classification appears to still be consistent with GHS. Finally, we have some suggested editorial changes to Table G.2 to clarify the correspondence between the GHS and NIOSH skin notation system. The suggested edits are incorporated in a revised Table G.2 that appears at the end of this review. NIOSH may also want to consider adding the GHS classification scheme for Specific Target Organ Toxicity for Repeated Exposures to show how that corresponds to the NIOSH system.	Additional information has been included within Appendix G.2 to further explain the differences between the NIOSH skin notation and the GHS scheme. Table G.2 has been updated to reflect the reviewers' suggestions. In regard to the use of the 1000 mg/kg-day cutoff value, the authors feel that the value is more conservative than the guidelines included within GHS and will be better for protecting the health of workers. No additional action taken.
5-4	Adverse Systemic Health Effects for SK-SYS - The document should clarify in section 2.2 (pg 7-8) that adverse respiratory, immune function, and other systemic effects that are the result of immediate or delayed immune hypersensitivity reactions are not assigned the notation. As discussed in section 2.4, these effects are assigned a SEN notation.	This issue has been addressed within Section 2.2. No additional action required.

Comment Number	Comment	Response (Action required)
5-5	Table 2.2 Paradigm for SYS notation - This table on page 13 needs some further discussion and clarification. If we are interpreting it properly, the table indicates that a chemical with (1) acceptable quality evidence of systemic toxicity from dermal exposure (e.g. animal study with NOAEL< 1000 mg/kg) and (2) quality evidence that there is insufficient dermal absorption to effectively contribute to the body burden (e.g. SI ratio < 0.1) is automatically assigned a SYS notation. On the other hand, the table indicates that the reverse situation in which a chemical with (a) quality evidence that there is sufficient dermal absorption to effectively contribute to the body burden and (b) acceptable quality evidence of no systemic toxicity from dermal exposure is automatically assigned a SKSTRIKEOUT. This seems to be a bit overly prescriptive and perhaps contradictory to the criteria in section 2.1, which argues for a weight of evidence approach when available data are inconsistent. It might be more prudent if table 2.2 clarify that a case-by-case judgment of the evidence is needed to determine a skin notation assignment in the two situations described above.	The reviewers have misinterpreted the information presented in Table 2.2. If no dermal absorption is available, but the data indicates that the chemical may cause systemic toxicity it would receive the SYS notation. If data indicates that it is absorbed, but the data indicates that no systemic effects are associated with skin exposure to the chemical it would not receive a SYS notation. This paradigm is consistent with the rationale discussed in section 2.2 and is intended to be included in the weight of evidence approach used to assign skin notations. No additional action taken.
5-6	SK-DIR(IRR) versus SK-DIR(COR) - Section 2.3 (pg 14-16) should make clear that a skin irritant is assigned SK-DIR(COR) when the appropriate corrosivity tests are positive and SK-DIR(IRR) when the corrosivity tests are negative (see appendix A-2). A skin irritant that is corrosive would not receive both SK-DIR(IRR) and SK-DIR(COR) notations as we read the draft CIB.	This issue has been directly addressed in Section 2.3. Additional information can be found in Appendix A-2. No additional action required.
5-7	SK-STRIKEOUT Notation - This notation is assigned when sufficient data were evaluated for a chemical and the evidence does not support a SYS, DIR, or SEN assignment. However, section 2.5 (pg 21-22) or appendix E.2 should clarify whether 'sufficient “data” refer to the quality of the individual data sets or to the completeness of the data across health endpoints, dose levels, and exposure durations or to all of the above.	An additional statement has been included within Appendix E.2 to indicate that the ranking refers to the overall quality and completeness of the data. No additional action required.

Comment Number	Comment	Response (Action required)
5-8	Dermal Absorption Cut-off Value - Appendix A.1 indicates that an estimated or predicted 10 percent absorption of the chemical applied to the skin is to be used as the cut-off for dermal penetration that contributes to the systemic dose. However, the appendix should make clear that the observed percentage of test chemical absorbed is critically dependent in almost any test protocol on the dose applied and vehicle used.	Additional information has been included in Section A.1.1 to indicate the role of factors discussed by the reviewers. No additional action required.
5-9	Dermal Absorption Algorithm - Appendix B incorporates previous suggestions on the dermal absorption algorithm provided by OSHA in early 2004 and is much improved. Section B.1.2 discusses the calculation of skin dose from a chemical in an aqueous liquid. NIOSH may also want to discuss the calculation of skin dose from exposure to an undiluted 'neat liquid' and skin exposure to solid particles since these chemical forms are fairly common in the occupational setting.	The model can be readily adapted to assess the neat compounds if dermal absorption and penetration data are available for the selected chemicals. Unfortunately, limited data of this time is currently available. A review of the limited data indicates that aqueous solution may represent a greater health hazard than neat substances. After review of Appendix B, the authors feel that sufficient information is included regarding the application of the dermal absorption algorithm. No additional action required.

Comment Number	Comment	Response (Action required)
5-10	Selecting and Prioritizing Candidate Chemicals – Appendix D lists several information sources that will be used to select candidate chemicals for classification. NIOSH may wish to consider a group of chemicals for which in vitro test data has recently become available as a result of a 2004 EPA test rule. These substances were identified as being of particular interest to OSHA. A summary of the dermal test results for this set of chemicals is available at Http://inside.mines.edu/Outreach/cont_ed/oeesc/P72.pdf.	This database has been included within Appendix E.1 as an informational source. The information will be evaluated when assigning skin notations to specific chemicals contained within the database. Additionally, NIOSH is in the process of working with EPA to obtain additional information on the database. No additional action required.

Comment Number	Comment	Response (Action required)
6-1	Appendix E; Page 65 & 66: Chemical Identification (ChemID): Redundant websites	Edit made; no additional action required
6-2	Page 67 The following link is dead (Web of Science)-New link http://thomsonreuters.com/products_services/scientific/Web_of_Science	New link inserted in document; all links referenced within document have been checked to ensure that they are active. No additional action required.
6-3	Page 95; Redundancy regarding Table F-1	Edit made; no additional action required
6-4	Page 96; Should g/L be grams per liter (not gallons/liter)?	Edit made; no additional action required
6-5	Page 112; Should read United Nations, not United Nation	Edit made; no additional action required
6-6	Page 114: Misspelling fullereness should read "fullerenes" (this error continues)	Edit made; no additional action required
6-1	Appendix E; Page 65 & 66: Chemical Identification (ChemID): Redundant websites	Edit made; no additional action required
6-2	Page 67 The following link is dead (Web of Science)-New link http://thomsonreuters.com/products_services/scientific/Web_of_Science	New link inserted in document; all links referenced within document have been checked to ensure that they are active. No additional action required.
6-3	Page 95; Redundancy regarding Table F-1	Edit made; no additional action required
6-4	Page 96; Should g/L be grams per liter (not gallons/liter)?	Edit made; no additional action required