# CPSC Staff Report on the Draft Proposed Revision of the FHSA "Strong Sensitizer" Supplemental Definition*

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**This report was prepared by the CPSC staff, and has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.*

# I. Introduction

The definition of "*strong sensitizer"* appears in section 2(k) of the Federal Hazardous Substances Act (FHSA) 15 U.S.C. §1262(k) and is restated in 16 CFR §1500.3(b)(9). The state of science has evolved since the U.S. Consumer Product Safety Commission (CPSC) added supplemental definitions in 1986 to the statutory definition.[1] In light of the ongoing United Nations (UN) mandate for the development of a globally harmonized system (GHS) to classify and label hazardous chemicals (including sensitizers), CPSC staff initiated a review of the definition of "strong sensitizer". A panel of scientists from academia, industry, and the federal government was convened to provide CPSC staff with scientific input. A series of questions regarding the sensitizer definition was submitted to the scientific panel and written responses were received by CPSC staff in the spring of 2005. The panel met on July 21, 2005, in a public session to discuss the definition and the rationale for potential changes. A decision was made to focus on potential revisions to the supplemental definitions since changes to the statutory definition would require Congressional action.

The purpose of this paper is to summarize the responses from the scientific panel, provide a rationale for proposed modifications to the existing supplemental definition, and propose a draft revised supplemental definition for "strong sensitizer". The Organisation for Economic Co-operation and Development (OECD) Expert Group which is also considering the definition of "sensitizer" and "strong sensitizer" for the GHS has planned an international workshop on current issues in skin sensitization risk assessment in October 2006 to discuss this issue.

# II. Background

## A. Federal Hazardous Substances Act

The FHSA became public law 86-613, Stat. 372, on July 12, 1960, as amended and codified at 15 U.S.C. §§1261-1278. The authority for the FHSA resided at the Food and Drug Administration (FDA) until it was transferred to CPSC in 1973. Congress enacted the FHSA to provide cautionary labeling for hazardous household substances. "Strong sensitizers" are one of the seven hazards defined under the FHSA. The definition of "*strong sensitizer"* which appears in section 2(k) of the FHSA (15 U.S.C. §1262(k); restated in 16 CFR 1500.3(b)(9)) is:

> *a strong sensitizer is a substance which will cause on normal*

[1] CFR 1500.3(c)(5)

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*living tissue through an allergic or photosensitive process a hypersensitivity which becomes evident on reapplication of the same substance and which is designated as such by the Commission. Before designating any substance as a strong sensitizer, the Commission, upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has significant potential for causing hypersensitivity.*

The FDA identified five substances as strong sensitizers[2]:

- paraphenylenediamine and products containing it
- powdered orris root and products containing it
- epoxy resin systems containing in any concentration ethylenediamine, diethylenetriamine, and diglycidyl ethers of molecular weight less than 200
- formaldehyde and products containing 1 percent or more of formaldehyde
- oil of bergamot and products containing 2 percent or more of oil of bergamot

Since its inception, CPSC has not designated any substances to be strong sensitizers. However, in 1986 the Commission issued a rule clarifying the FHSA's "strong sensitizer" definition with supplemental definitions as recommended by a Technical Advisory Panel on Allergic Sensitization (TAPAS)[3]. The following supplemental definitions were intended to clarify the interpretation of the statutory definition for a "strong sensitizer":

*- Sensitizer: A sensitizer is a substance that will induce an immunologically-mediated (allergic) response, including allergic photosensitivity. This allergic reaction will become evident upon re-exposure to the same substance. Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization.*

*- Strong: In determining that a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors. These factors should include any or all of the following (if available):*

- *Quantitative or qualitative risk assessment*
- *Frequency of occurrence and range of severity of reactions in healthy or susceptible populations*

[2] 16 CFR §1500.13

[3] 16 CFR §1500.3(c)(5)

- *The result of experimental assays in animals or humans (considering dose-response factors), with human data taking precedence over animal data*
- *Other data on potency or bioavailability of sensitizers*
- *Data on reactions to a cross-reacting substance or to a chemical that metabolizes or degrades to form the same or a cross-reacting substance*
- *The threshold of human sensitivity*
- *Epidemiological studies*
- *Case histories*
- *Occupational studies*
- *Other appropriate in vivo and in vitro test studies*

*- Severity of Reaction: The minimal severity of a reaction for the purpose of designating a material as a "strong sensitizer" is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:*

- *physical discomfort*
- *distress*
- *hardship*
- *functional or structural impairment*

*These may, but not necessarily, require medical treatment or produce loss of functional activities.*

*- Significant potential for causing hypersensitivity: "Significant potential for causing hypersensitivity" is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance, documented medical evidence of allergic reactions obtained from epidemiological surveys or individual case reports, controlled in vitro or in vivo experimental assays, or susceptibility profiles in normal or allergic subjects.*

*- Normal living tissue: The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory or gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion or inhalation.*

For a product containing a strong sensitizer to be designated a hazardous substance and to require cautionary labeling under the FHSA[4], the product must be capable of causing substantial personal injury or substantial illness during or as a result of customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion

[4]The FHSA, 15 U.S.C. 1261(p), requires cautionary labeling for any article intended or packaged for household use if it contains a hazardous substance.

by children[5]. This requires consideration of the route and the level of exposure that can be expected to be presented by the strong sensitizer as it exists in the particular substance. Therefore, the determination of whether a cautionary label is required is made on a product-by-product basis and is not solely based upon the presence of a strong sensitizer in a product. If a substance containing a strong sensitizer is determined to be a hazardous substance under the FHSA, cautionary labeling, including the signal words "Caution" or "Warning" and an affirmative statement such as "May Produce Allergic Reaction By Skin Contact" could be required.[6] While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic hazards, the manufacturer is required to label a product appropriately according to the FHSA requirements. However, if a toy or other article intended for use by children is a hazardous substance, then the product is by definition a banned hazardous substance unless specifically exempted[7].

In addition, Congress amended the FHSA in 1988 to include the Labeling of Hazardous Art Materials Act (LHAMA) requirements. The LHAMA requires a reviewing procedure for developing precautionary labels for all art materials. This amendment to the FHSA concerns chronic health hazards known to be associated with a product or product component when present in a physical form, volume or concentration that presents the potential to produce a chronic health hazard as determined by a toxicologist. Within the regulation under the Act, a "sensitizer" is defined as *a substance known to cause, through an allergic process, a chronic adverse health effect which becomes evident in a significant number of people on re-exposure to the same substance*[8]. To protect users from known sensitizers found within art materials, each label shall contain a list of those sensitizers present in sufficient amounts to contribute significantly to a known skin or respiratory sensitization.[9]

[5] 16 C.F.R. §1500.3(b)(4)(i)(A)
[6] Congress, in enacting the FHSA, did not intend that precautionary labeling be required on all products. A strong sensitizer must be a substance that affects a significant portion of the population and produces substantial illness. Report No. 1158, Calendar No. 1197, March 10, 1960; 86th Congress. *Hazardous Substances for Household Use*.
[7] 16 C.F.R. §1500.3(b)(15)(i)
[8] 16 C.F.R. §1500.14(b)(8)(i)(B)(9)
[9] 16 C.F.R. §1500.14(b)(8)(i)(E)(5)

## B. Globally Harmonized System of Classification and Labeling of Chemicals (GHS)[10]

In 1992, during the United Nations Conference on Environment and Development (UNCED), a mandate was established for the development of a globally harmonized system (GHS) to classify and label hazardous chemicals. Under the GHS, the term "chemical" includes substances, mixtures and preparations.

The objective of GHS is to harmonize the classification and labeling of chemicals to ensure safe use, transport and disposal on an international basis. In general, the mandate stated that classification criteria are to be developed on the basis of existing validated data based upon internationally recognized scientific principles "*with a clear distinction between classes and categories*". Three parameters were agreed upon by the Coordinating Group for the Harmonization of Chemical Classification Systems (CG/HCCS) and considered critical to the application of the global harmonization system to all chemical hazards, including sensitizers. The first parameter stated that, "*the GHS covers all hazardous chemicals. The mode of application of the hazard communication components of the GHS (e.g. labels) may vary by product category or stage in the life cycle. Target audiences for the GHS include consumers, workers* …" The second parameter indicated that, "*the GHS does not include establishment of uniform test methods or promotion of further testing to address adverse health effects*." The last parameter stated that, "*in addition to animal data and valid in vitro testing, human experience, epidemiological data, and clinical testing provide important information that should be considered in application of the GHS*."

At this time, the general GHS hazard classification of a chemical incorporates three steps[11]: the identification of relevant data, the review of that data, and the determination of whether the substance can be classified as a hazard and its degree of hazard.

The GHS deals with respiratory sensitizers and skin sensitizers independently. The GHS definition for a respiratory sensitizer is, "*a substance that will induce hypersensitivity of the airways following inhalation of the substance*." The GHS then indicates that, "*substances shall be classified as a respiratory sensitizer in accordance with the following criteria: if there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or if there are positive results from an appropriate animal test*." The GHS guidance on what constitutes human evidence for respiratory sensitization indicates that,

[10] Globally Harmonized System of Classification and Labeling of Chemicals (GHS), United Nations, New York and Geneva, 2003.
[11] GHS, Section 1.3.2.2.2

"*evidence that a substance can induce specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered.*[12] *The condition will have a clinical character of an allergic reaction. However, immunological mechanisms do not need to be demonstrated*."

It would appear that the GHS uses the term "respiratory" as an inclusive term, representing not only the upper (e.g., rhinitis) and lower respiratory tracts, but also conditions (e.g., conjunctivitis) which frequently accompany respiratory hypersensitivity.

The GHS provides further guidance when considering human evidence, that it "*is necessary for a decision on classification to take into account, in addition to the evidence from the cases, the size of the population exposed and the extent of exposure*." "*The evidence referred to above could be: clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include: in vivo immunological test (i.e. skin prick test); in vitro immunological test (i.e. serological analysis*[13]*); studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven …; and a chemical structure related to substances known to cause respiratory hypersensitivity*."

In addition, evidence "*could be data from positive bronchial challenge tests*" which is later indicated as acceptable as a stand-alone determinant for classification. Data from appropriate animal studies "*may include measurements of IgE levels and other specific immunological parameters, and, specific pulmonary responses in guinea pigs*."

The GHS definition for a "skin sensitizer" is "*a substance that will induce an allergic response following skin contact*." Substances shall be classified as contact sensitizers "*if there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or, there are positive tests from an appropriate animal test."* In the GHS guidance on what constitutes evidence for skin sensitization, it is indicated that *"evidence should include any or all of the following: positive data from patch testing …; epidemiological studies showing allergic contact dermatitis by the substance; situations in which a high proportion*

[12] Rhinitis is inflammation of the nasal mucosa and conjunctivitis is inflammation of the conjunctiva, the membrane which lines the inner surface of the eyelid as well as the sclera, the white part of the eye. Conjunctivitis can have many causes (e.g. viral, bacterial, fungal, irritant), one of which is allergic. Alveolitis is inflammation of the alveoli, the section in the lung where air exchange occurs.

[13] Serological analysis involves testing serum for the presence of factors involved in the allergic process such as eosinophil cells, elevated total immunoglobulin E (IgE) levels and antigen specific antibodies.

*of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small; positive data from experimental studies in man, well documented episodes of allergic contact dermatitis…; positive data from appropriate animal studies*."

"*For animal studies utilizing adjuvants*[14] *at least 30% of the animals must be responsive in order for the substance to be considered positive as a sensitizer, for non-adjuvant studies at least 15% of the animals must be responsive. Appropriate tests would include the guinea pig maximization test [GPMT], Buehler guinea pig test (Buehler Assay, BA), and local lymph node assay [LLNA]. The mouse ear swelling test [MEST] could be utilized as a first stage test in the assessment of skin sensitization potential*."

The GHS provides guidance for classification of a substance as a skin sensitizer if none of the aforementioned conditions for evidence is met. A case-by-case basis can be followed if two or more of the following indicators occur: "*isolated episodes of allergic contact dermatitis; epidemiology studies of limited power…; data from animal tests… which do not meet the criteria for a positive result … but which are sufficiently close to the limit to be considered significant; positive data from non-standard methods; and positive results from close structural analogues*."

A central dogma of sensitization that most immunologists believe is that the ability of a chemical to cause sensitization is a dose-dependent phenomenon[15]. Generally, the greater the level of exposure (i.e., dose), the more vigorous will be the induced immune response and the greater the level of sensitization. In addition to dose, the ability of a chemical to cause sensitization can also be linked to its physico-chemical properties. These help determine the chemical's "potency" as a sensitizer or allergen.

For weaker allergens, sensitization will require exposure to larger amounts than is necessary for sensitization to stronger allergens (Appendix A). For skin sensitizers, the GHS indicates that, "*for the purpose of hazard classification it may be preferable to distinguish between strong and moderate sensitizers. However, at present animal or other test systems to subcategorize sensitizers have not been validated and accepted. Therefore, sub-categorization should not yet be considered as part of the harmonized classification system*."

A 2002 UN mandate[16] directed the OECD to consider use of "strong versus weak" sensitizers in the GHS. This mandate was extended for the

[14] Adjuvants are substances that are added in the presence of an allergen to boost the intensity of the immune response. Common adjuvants are alum, complete Freund's adjuvant (CFA), and incomplete Freund's adjuvant (IFA).
[15] Kimber I et al,Toxicological Sciences 2001, 59:198-208.
[16] ST/SG/AC.10/C.4/2002/19, December 2002, UN Sub-Committee HCL

biennium 2005-2006. The stated objective of the mandate is "*to examine the available information concerning strong vs. weak sensitizers and, if appropriate, propose revisions to the classification criteria for respiratory and/or dermal sensitization*." One proposal to the OECD Expert Group by a group of European constituents is to consider a multi-class categorization for chemical sensitizers based upon potency (e.g., weak, moderate, strong, and extreme). Some of the current issues the OECD Expert Group is addressing for this mandate are: (1) the development of a scientifically defensible way to define strong versus weak sensitizers with sufficient clarity for classification purposes; (2) that the harmonization effort takes into consideration existing hazard-based systems; (3) that harmonized categories are strongly differentiated such that substances can be classified consistently in the various UN nations; (4) that classification should be able to be used for both existing and new chemicals; and (5) that the advantages/disadvantages of utilization of either animal data or human data be determined in relation to the requirements of the GHS which is based on hazard classification[17].

## C. CPSC Staff's Sensitizer Scientific Panel – July 2005

A scientific panel was convened in 2004-2005 by CPSC staff to address the definition of *"strong sensitizer"* which appears in section 2(k) of the Federal Hazardous Substances Act (restated in 16 CFR 1500.3(b)(9)) and supplemented in section 1500.3(c)(5). The statutory definition and supplementary amendments have not been reviewed since 1986 and the state of the science has advanced since then. The panel was comprised of six scientists from Federal agencies, academia and industry, each with regulatory, research and/or clinical experience with chemical and protein sensitizing agents. The scientific panel members were Dr. Michael Luster (National Institute of Occupational Safety and Health), Dr. MaryJane Selgrade (U.S. Environmental Protection Agency), Dr. Frank Gerberick (Proctor and Gamble Company), Dr. James Taylor (The Cleveland Clinic), Dr. David Bernstein (University of Cincinnati College of Medicine), and Dr. David Basketter (Unilever Safety and Assurance Centre).

The objective of the panel was to examine the available information concerning sensitizers (respiratory and skin) and, if appropriate, to propose revisions to the existing FHSA definition for sensitization based on their knowledge as scientific experts in this field. To meet these objectives, CPSC staff prepared a set of questions to which each panel member responded in writing. The panel was to make suggestions regarding (1) classification criteria for a sensitizer, taking into account the GHS definition of sensitizers, (2) what testing/data CPSC should accept

[17] Request for Declassification of HCL Document: Draft Scientific Issue Paper on Strong vs. Weak Sensitizers, March 22, 2006; OECD.

for the determination of sensitizing ability, and (3) the risk assessment process for a sensitizer, particularly with regard to child versus adult sensitivity and the existence of threshold responses in those populations. The panel met on July 21, 2005, to discuss their compiled responses to the questions CPSC staff sent to them in advance of the meeting.

## III. CPSC Staff Questions Posed to the Expert Scientific Panel

The first question posed to the panel members focused on potential revisions to the FHSA statutory definition and supplemental definitions of "strong sensitizer". Whereas the FHSA definition addresses only a single category of sensitizer (i.e., "strong"), the GHS Expert Group for sensitization is considering a multi-class categorization for chemical sensitizers based upon potency (e.g., weak, moderate, strong, and extreme). Therefore, the second question to the panelists asked them to consider whether additional classification categories should be incorporated into the FHSA definition of a sensitizer. The last three questions presented to the panelists concerned ongoing issues in the field of immunotoxicology with regard to sensitization (e.g., validated and appropriate tests for identifying sensitizing substances, children as a susceptible population, and chemical matrix effects[18]). The responses to the last three questions are relevant for the CSPC staff's risk assessment of sensitization once a chemical/substance has been declared as a "strong sensitizer" (i.e., the hazard identification step).

The following section is a summary based upon the discussion at the July 21st meeting and the written responses to the staff questions submitted by the panelists. For each question, a summary of the panel discussion is preceded by the specific question in bold face type; CPSC staff comments follow the panelists' discussion. The current statutory and supplemental definitions for "strong sensitizer" are in italic type.

### A. Question #1

**Taking into account the GHS definition concerning sensitizers (respiratory and skin) and current scientific information, should the FHSA statutory definition of "strong sensitizer" and/or the guidance or its interpretations be revised? If so, state why and what revisions would be suggested. Cite relevant documentation to support the revision.**

[18] The exposure of the general population to a sensitizing chemical in consumer products is less likely to be to the pure chemical but rather to the chemical as part of a mixture. A chemical matrix is the formulation in which the sensitizing agent is present. The matrix components can enhance the sensitizing capability of a substance. For example, surfactants, a broad class of chemicals, are common in consumer products as processing agents and detergents. Surfactants such as sodium lauryl sulfate are known to enhance the allergenicity of some chemicals.

**Panel Discussion**

Each panel member recommended that the definition be revised, though to varying degrees. The overall discussion points regarding the "strong sensitizer" definition are summarized below. In the subsequent sections there is a step-by-step review of each subsection of the supplemental definitions (e.g., *i-sensitizer, ii-strong, iii-severity of reaction, iv-significant potential for hypersensitivity, and v- normal living tissue*). For each subsection, the panel's discussion is described followed by the CPSC staff summary of the issues.

The panelists discussed the use of the term "strong" which they felt implied a comparison, although no basis for a comparison was provided in the statutory definition. One panelist suggested dropping the word "strong" and utilizing a more classical definition incorporating the stages of the sensitizing process:

> "*A sensitizer is a substance or a photoactivated substance that causes tissue damage by inducing excessive or inappropriate antibody or cell-mediated immune responses (hypersensitivity). These adverse effects are the result of a two stage process: 1) Induction (sensitization) requires a sufficient or cumulative exposure dose of the sensitizing agent to induce immune responses that initially produce no or few symptoms; 2) Elicitation occurs in a sensitized individual upon subsequent exposure to the substance and results in overt symptoms."*

This suggestion would act as a replacement for both sections *i (sensitizer)* and *ii (strong)* of the supplemental definitions. However, this was not supported by the full panel. The definition provided for "strong sensitizer" in the statute is one that the panel felt would be considered by the scientific community to define any sensitizer. A decision was made to focus on potential revisions to the supplemental definitions since changes to the statutory definition would require Congressional action. Therefore, the panel did not make any suggestions concerning the statutory language.

The panelists were asked to review the FHSA and supplemental definitions while also considering the GHS definitions. The panel, therefore, began their discussion with an evaluation of the GHS definitions. Some panelists expressed concern that the GHS only defined respiratory and skin sensitizers (Type I and Type IV sensitizers; Appendix A), thus limiting consideration of other routes of exposure such as ocular exposure. Several panelists felt that human exposure determinants (e.g., duration, exposure site, frequency and genetic variability) were not sufficiently considered in the GHS definition. Furthermore, they noted that the GHS does not consider severity of reaction.

Since the GHS focus on classification is hazard-based and allows for the labeling to be either hazard or risk-based, some panel members expressed concern that products posing little or no risk would also be labeled under the GHS.

**CPSC Staff Summary**

In agreement with the panelists, CPSC staff believes that revisions should be made to the supplemental FHSA definition to clarify the terminology referring to the allergenicity and risk associated with a chemical.

For the term "strong", it was suggested that more specific, and if available, more quantitative criteria be provided for what designates a sensitizer as "strong" versus "weak". One panelist suggested dropping the word "strong" and utilizing a more classical definition incorporating the stages of the sensitizing process. The other panelists did not agree with this suggestion nor does the CPSC staff. The FHSA supplemental definition (*i*) for "sensitizer" is reflective of the classical definition, including both the induction (sensitization) and elicitation stages. Furthermore, by excluding the word "strong" from the definition, the number of chemicals that could be declared as sensitizers would be vastly increased, as would the number of products that could require labeling. The intent of the FHSA is to address only a subset of sensitizers, those having a significant health impact.

The panelists did not suggest modifications to the supplemental FHSA definition of "strong sensitizer" in order to harmonize with the GHS definitions of respiratory and skin sensitizers. The panelists believed the FHSA definition was a more comprehensive definition than the GHS definitions.

**Supplemental Definitions**

(i) *Sensitizer.*

*A sensitizer is a substance that will induce an immunologically-mediated (allergic) response, including allergic photosensitivity. This allergic reaction will become evident upon re-exposure to the same substance. Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization* (Appendix A, general background on sensitization).

**Panel Discussion**

As part of the supplemental definition, a sensitizer is defined as a "*substance that will induce an immunologically-mediated response*…" The panelists discussed the fact that some substances (e.g., the chemical

class of isocyanates) have no defined Immunoglobulin E (IgE) responses, but exhibit the other immunologically-mediated characteristics of sensitizers and therefore are classified as sensitizers based upon these other characteristics[19]. The panelists also talked about other chemicals that do not appear to be allergic sensitizers, but upon *in vivo* or *in vitro* testing, demonstrate an immunologically-mediated response. The panelists felt that leaving the term "immunologically-mediated" without additional definition was preferable to changing this part of the definition even though there are some sensitizers that may not demonstrate an obvious "immunologically-mediated" response.

The panelists noted that in the future with progress in the science, there may be a need to have a definition for each class of allergen based on target organ (e.g., respiratory, ocular and skin) or functional class (e.g., protein, chemical). This would be somewhat similar to the GHS definition which has separate definitions for respiratory and dermal (skin) sensitizers. However, the panelists did not make such a suggestion at this time since insufficient evidence exists to clearly separate the sensitization characteristics (e.g., mechanisms of sensitization) of the different target organs.

The consensus of the panelists on the last sentence of this paragraph was to revise this sentence and move it to section (*ii*) so as not to imply that "sensitizer" includes what could be an "irritant response"[20]. More frequently the response (symptoms) that is noted after the first exposure is an irritant response and not an allergic response. Typically allergic responses are the result of a two step process: (1) induction (sensitization) which requires sufficient or cumulative exposure (dose) to induce an immune response with few or no symptoms and, (2) elicitation when an individual who has been sensitized demonstrates symptoms upon subsequent exposure.

The suggested revised sentence would read, "Occasionally, a sensitizer will apparently induce and elicit an allergic response on first exposure". The panelists concurred that "apparent" simultaneous sensitization and elicitation can sometimes occur with strong sensitizers and therefore the phrase would more appropriately fit in section (*ii*) *strong*. They suggested that, "apparent" takes into account scenarios where the "first" exposure may actually not be the first exposure but one in which there may have been a prolonged exposure, where previous exposures were not noted, or where previous exposures produced few or no symptoms.

[19] The production of IgE antibodies is typical of Type I hypersensitivity reactions (e.g., rhinitis, urticaria). See Appendix A.

[20] An "irritant response" is a non-immune mediated response and one that results from direct injury to the tissue. An irritant is any agent that is capable of producing cell damage in any individual if applied for sufficient time and concentration.

**CPSC Staff Summary**

CPSC staff concurs with the panelists to not further define the term "immunologically-mediated". Trying to further define "immunologically-mediated" would create the potential for exclusion of substances which sensitize through atypical mechanisms. However, the weight of evidence approach suggested by CPSC staff to be included in the draft proposed supplemental definitions for the determination of the sensitizing strength of a substance should ensure that these substances will be captured.

Furthermore, the presence of an immune-mediated response is what separates an allergic response from that of an irritant response.

The focus of the panelists on the presence/absence of an IgE response is that the immune mechanism most commonly associated with an allergic response is the presence of specific IgE antibodies to the allergenic substance[21]. However, specific IgE antibodies can be very difficult to detect and can be masked by the presence of other classes of antibodies. When specific antibodies cannot be detected, other characteristics are used to designate a chemical as a sensitizer. These include the length of time it takes for symptoms to occur and the dose at which symptoms occur.

CPSC staff agrees with the panelists that the last sentence of this paragraph, "*Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization",* could cause confusion and should be removed from this section. In order for an individual to become sensitized to a particular substance, it typically takes time and multiple exposures for the sensitization to become evident. The amount of time and the amount of exposure (the dose) required for sensitization will depend upon the individual. In the scientific community, it is generally considered that it takes months to years for sensitization to develop. It is extremely rare to have "simultaneous sensitization and elicitation"; a strong response upon first exposure is typically considered to be an irritant response and not an allergic reaction. Individuals who are sensitized but do not exhibit clinically detectable sensitization (i.e., do not exhibit symptoms) when challenged are characterized as having "subclinical sensitization". When challenged a second time in a clinical setting, these individuals will then have a very strong response. Therefore, the phrase "variable period of exposure" will be included in the draft proposed definitions to reflect the latency period which is a characteristic in the development of sensitization.

[21] Total IgE levels are also associated with allergic diseases. Asthma prevalence has been shown to be associated with increased levels of total IgE, even in individuals who have tested negative for specific IgE to common allergens and in non-atopic individuals. IgE has been shown to play a central role in seasonal allergic rhinitis, atopic dermatitis, latex allergies, food allergies, anaphylaxis and urticaria.

Irritant responses occur without sensitization. An irritant is any agent that is capable of producing cell damage in any individual if applied for sufficient time and concentration. Irritants include substances and activities such as water, detergents, solvents, acids, alkalis, adhesives and friction. Some mild irritants may require prolonged or repeated exposure before symptoms occur, while other irritants can produce an immediate reaction and may even resemble a thermal burn. Most cases of irritant contact dermatitis are mild. Irritant symptoms can occur within minutes of the exposure, while allergic reactions (e.g., type IV hypersensitivity) may take 6 to 24 hours to produce symptoms. Furthermore, irritant symptoms are localized to the area of contact while allergic responses (e.g., allergic contact dermatitis) may spread over time.

CPSC staff believes it is not necessary to include the suggested revised sentence "Occasionally, a sensitizer will apparently induce and elicit an allergic response on first exposure" in either section (i) or section (ii) of the supplemental definition. Inclusion of this sentence in the supplemental definitions would likely continue to provide the opportunity for misinterpretation and inclusion of irritant substances within the category of "strong sensitizers".

The CSPC staff draft proposed **revision of section** (*i*) would read:

> *Sensitizer.* A sensitizer is a substance that will induce a state of immunologically-mediated hypersensitivity (including allergic photosensitivity) following a variable period of exposure to that substance. Hypersensitivity to a substance will become evident by an allergic reaction elicited upon re-exposure to the same substance.

**Supplemental Definitions -**
(ii) *Strong.*

*In determining that a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors. These factors should include any or all of the following (if available):*

- *Quantitative or qualitative risk assessment*
- *Frequency of occurrence and range of severity of reactions in healthy or susceptible populations*
- *The result of experimental assays in animals or humans (considering dose-response factors), with human data taking precedence over animal data*
- *Other data on potency or bioavailability of sensitizers*

- *Data on reactions to a cross-reacting substance or to a chemical that metabolizes or degrades to form the same or a cross-reacting substance*
- *The threshold of human sensitivity*
- *Epidemiological studies*
- *Case histories*
- *Occupational studies*
- *Other appropriate in vivo and in vitro test studies*

**Panel Discussion**

The panelists agreed that while the supplemental definition expands and provides factors to be considered in the determination of "strong" and "severity of reaction", many of these factors are subjective (physical discomfort, distress, hardship) and not quantitative.

The panelists stated that a weight of evidence approach should be used to determine the strength of a sensitizer.

In defining a strong sensitizer, the supplemental definition states that available data on a number of factors should be considered. The first of these factors is "*quantitative or qualitative risk assessment*". The examples given by the panelists indicating how such data could be utilized suggested the use of both potency and exposure. The following describes what the panelists suggested:

- For a less potent allergen, exposure would be a determining factor in whether that substance is a significant sensitizer and whether the product should be labeled.
- For a more potent allergen, the potency is the more critical factor since less exposure is needed for a potent allergen to cause sensitization.
- For a substance which is highly potent in animal studies, but for which no human exposure data is available, an exposure assessment would be needed to determine bioavailability and risk.

For *frequency of occurrence*, the panelists suggested that a numerical threshold (i.e., cutoff) be provided. This threshold would function as a guide for when frequency of occurrence is significant for the determination and labeling of a substance as a "strong sensitizer". The panelists concurred that the frequency of allergy is a function of the nature and extent of allergen exposure, not just of allergen potency. The European Union considers a substance to be a strong sensitizer if the frequency of sensitization to that substance in the general population is greater than or equal to 1%. The U.S. scientific community in its discussions regarding a protective threshold for strong sensitizing agents has not agreed on a

specific level of sensitization in the general population. Questions have been posed whether protecting 90% or 95% of the general population is sufficient and/or appropriate[22]. For the determination of a threshold value, some of the panelists indicated that data exists for chemicals (e.g., isocyanates, colophony, plicatic acid) which could be utilized as benchmarks for estimating an appropriate frequency of occurrence in the general population. For protein allergens, latex data could be used as a benchmark. However, the threshold value is likely allergen dependent. The panelists discussed examples of weaker sensitizers which have wide exposure in the general population (e.g., nickel) as well as strong allergens with low or rare population exposures.

The panel also discussed the term "*severity of reaction*" and how it might be better defined. It was suggested by several panelists that the American Medical Association's (AMA) *Guides to the Evaluation of Permanent Impairment*[23] be used to provide objective criteria for evaluating the severity of a reaction in the respiratory system and skin (Appendix B).

The panelists suggested that a definition for *bioavailability* should be provided.

The panelists believed that the remaining factors listed in this section of the definition should be ranked in order of importance, instead of "any or all". The suggested ranking would be:

- Validated clinical and diagnostic studies
- Epidemiological studies
- Occupational studies
- Well-conducted animal studies
- *In vitro* studies
- Cross-reactivity data
- Case histories

The panelists based their suggestion for ranking on precedence for human data over animal data.

Furthermore, the panelists recommended that Quantitative Structure-Activity Relationships (QSARs), *in silico* data, and relative potency, be added as additional considerations.[24]

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[22] HESI Immunotoxicology Technical Committee, Respiratory Hypersensitivity Workshop, Washington, DC, June 2004.

[23] *Guides to the Evaluation of Permanent Impairment, 5th Edition, AMA Press, 2001*

[24] QSARs or Quantitative Structure-Activity Relationships are mathematical models that relate a quantitative measure of chemical structure to biological activity. *In silico* data is a computational approach using sophisticated computer models for the determination of a sensitizing potential. QSARs

**CPSC Staff Summary**

The panelists stated that a *weight of evidence* approach should be used to determine the strength of a sensitizer. CPSC staff agrees and will include this modification to the supplemental definitions in the CPSC staff draft proposed definitions.

In defining a strong sensitizer, the supplemental definitions state that available data on a number of factors should be considered. The first of these factors is "*quantitative or qualitative risk assessment*." CPSC staff believes that the terminology of "qualitative or quantitative risk assessment" is a source of confusion in the interpretation of the supplemental definition because it places a risk assessment step within the hazard identification step of the overall paradigm. Qualitative and quantitative assessments are inherent in the weight of evidence approach (e.g., utilizing the listed criteria) proposed by CPSC staff for inclusion in the draft supplemental definition.

Currently, after CPSC has designated that a particular chemical is a "strong sensitizer" (essentially the hazard identification step), staff could begin the risk assessment process by determining whether exposure to that product (taking into account bioavailability and dose) is such that it could result in sensitization. If exposure to the product containing the sensitizer would cause sensitization, then labeling could be required or the product could be banned if it were a children's product.[25]

In the examples provided by the panelists on how data could be used for the "quantitative or qualitative risk assessment" process, emphasis was placed on exposure data (in this case, population data) and frequency of use such that less potent allergens could also be considered as "strong sensitizers". These examples place risk assessment considerations into the hazard identification step.

The remaining factors listed in this section have the potential to provide sufficient information for determining the potency of a substance; i.e., its ability to be a "strong sensitizer". CPSC staff believes that the presence of "qualitative and quantitative assessment" does not strengthen the supplemental definition and removal would reduce potential misinterpretation of the definition. Therefore, CPSC staff believes that

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and *in silico* approaches are evolving methodologies that have not yet been validated. These techniques are being pursued to reduce the numbers of expensive laboratory (*in vitro*) and animal (*in vivo*) experiments carried out.

[25] While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic hazards, the manufacturer is required to label a product appropriately according to the FHSA requirements.

"qualitative or quantitative assessment" should be removed from the supplemental definitions.

During the discussion on ***frequency of occurrence***, the panelists suggested that a numerical ***threshold*** (i.e., cutoff) be provided. This threshold would function as a guide for when frequency of occurrence is significant for the determination and labeling of a substance as a "strong sensitizer".

The list of chemicals provided by the panelists is a list comprised predominantly of occupational sensitizers. Because the degree of sensitization in the workplace is likely greater than that of the general population due to greater exposure (both in time and concentration) to the sensitizing agent, CPSC staff believes that it is inappropriate to apply work-related frequencies of chemical sensitization to the consumer scenario. For example, the prevalence of latex allergy in healthcare workers ranges from 2.2 to 17 percent, for spina bifida patients prevalence ranges from 29 to 65 percent, and the prevalence for the general population is estimated to be below one percent.[26]

Data for the determination of a threshold value of sensitivity for the general population is limited since most epidemiological studies are performed on a subset of the general population, that is, on individuals who are already sensitized. The European Union considers a substance to be a strong sensitizer if the frequency of sensitization to that substance in the general population is greater than or equal to 1 percent. It is generally accepted by the scientific community that allergic contact dermatitis affects 1 percent of the general population worldwide. The Institute of Medicine (IOM) in their executive summary on indoor allergens indicated that 20 percent of the general population will develop an allergy-related illness (sinusitis, rhinitis, bronchitis, asthma)[27]. However, with the rate of allergy in industrialized countries dramatically increasing over the past two decades and with prevalence factors likely varying for each sensitizing agent, setting a threshold value for a "strong sensitizer" at 1 percent may be either overly protective or insufficiently protective. CPSC staff believes that the determination of a threshold sensitization level for defining a "strong sensitizer" is best considered on a case-by-case basis.

During the discussion regarding the term "***severity of reaction***" and how it might be better defined, it was suggested by several panelists that the AMA's *Guides to the Evaluation of Permanent Impairment* be used to

[26] CPSC (2003) – "Petition on Natural Rubber Latex (HP 00-2)." Memorandum from J Elder and S Barone to The Commission, Todd Stevenson. October 10, 2003.
[27] IOM (Institute of Medicine), 1993. *Indoor Allergens: Assessing and Controlling Adverse Health Effects.* Washington DC, National Academy Press.

provide objective criteria for evaluating the severity of a reaction in the respiratory system and skin (Appendix B). These guidelines are used worldwide and are designed to bring objectivity to an area of great subjectivity by providing clinically sound and reproducible criteria for defining levels of impairment. In the United States, the majority of the states utilize the AMA guidelines in the context of worker compensation issues. It is formally accepted through adoptive language by states and by the US Congress (e.g., the Federal Employee's Compensation Act [FECA]).

To define degrees of impairment, the AMA guidelines focus primarily on loss of function and the impact on daily living activities. The level of detail and severity of injury found in the AMA guidelines is more stringent than what is listed in the current FHSA "strong sensitizer" supplemental definition. The AMA defines impairment as "*a loss, loss of use or derangement of any body organ part, organ system or organ function*". A medical impairment can develop from an illness or injury. The impairment is considered permanent when little medical improvement in the condition is seen after a year's time. Permanent impairment requires a medical assessment by a clinician. The guidelines provide values assigned to levels of functionality starting with the normal or "pre-existing state". These tables provide ranges of values that take into account age and gender, etc.

The other major focus of the AMA assessment for impairment is the impact on common activities of daily living (ADL). ADL includes self-care (personal hygiene), communication (e.g., speaking, seeing), physical activity (e.g., walking, standing), sensory function (e.g., smelling), non-specialized hand activities (e.g., grasping), travel, sexual function and sleep. Work tasks are not considered in making this determination because of the difficulty in accounting for the diversity and range of complexity of work.

CPSC staff believes that the AMA approach to defining levels of impairment is more detailed and rigorous than what is encompassed in the FHSA "strong sensitizer" supplemental definitions. However, the AMA guidelines along with similar approaches to defining and categorizing levels of impairment from other Federal agencies (e.g., Veterans Administration, Social Security Administration)[28] provide approaches that

[28] The system developed by the Social Security Administration (SSA) for determining benefits is similar to the AMA guidelines except that the focus is on the inability to work due to a medical condition. An impairment is considered "*severe enough*" when it prevents an individual from performing "*any gainful activity*." The SSA provides a list of impairments (Blue Book, publication 64-039, January 2005) which are considered so severe that the individual is, by law, automatically defined as disabled. Similar to the AMA guidelines, the impairment must last, or be expected to last, for at least 1 year, or result in death. Impairment is determined by "*medically accepted clinical and laboratory diagnostic techniques*"; a

CSPC staff could utilize as a basis for developing similar guidelines for interpreting the supplemental definitions. The CPSC staff draft proposed guidelines could utilize the data listed in section (*ii*) and place more emphasis on medical evaluation for the determination of the severity of reaction (Appendix C).

The panelists suggested that a definition for ***bioavailability*** be provided. CPSC staff agrees and will include this modification to the supplemental definitions in the CPSC staff draft proposed definition. Bioavailability is the dose of the allergen available to interact with a tissue. It is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical.[29]

CPSC staff suggests eliminating the words "*in vivo*" from the last factor, "*other appropriate in vivo and in vitro test studies*", since it is redundant with the other factors referring to animal and human studies ("validated clinical/diagnostic studies, epidemiological studies, occupational studies, and case histories").

CPSC staff concurs with the panelists' suggestion to rank and list the remaining qualifying factors in order of importance, instead of "any or all". This suggestion for ranking is based on precedence for human data over animal data. The supplemental definitions have separate qualifiers for occupational studies and epidemiological studies. Occupational studies, by definition, would be considered a subset of epidemiological studies. CPSC staff believes it is important to include both types of studies in the proposed supplemental definitions. However, both studies should be in the same qualifier and with the indication that epidemiological studies (general population studies) are preferred over occupational studies. As discussed earlier in this section, the degree of sensitization in the workplace is likely greater than that of the general population due to greater exposure (both in time and concentration) to the sensitizing agent. Therefore, although providing helpful information regarding the potential

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physical impairment "*must be established by medical evidence consisting of signs, symptoms and laboratory findings, not only by the individual's statement of symptoms*."

[29] Consideration of bioavailability typically falls outside the hazard identification step. However, bioavailability data can be useful when evaluating the applicability and validity of the human and animal data utilized in the hazard identification step. Assessment of bioavailability is typically considered in determining whether a chemical/substance presents a hazard under reasonably foreseeable handling or use (i.e., whether it is a hazardous product). As stated in the Chronic Hazard Guidelines, it is an individual's exposure to the toxic component (chemical) or the bioavailability of the component (chemical) which is considered to reflect the significant risk of the substantial adverse health effect associated with use of the product. "The need to consider bioavailability in estimating the risk from use of a product containing a toxic substance only arises when it is anticipated that the absorption characteristics of a substance to which there is human exposure will differ from those characteristics for the substance tested in the studies used to define the dose-response relationship." 16 CFR §1500.135(d)(2)

sensitizing strength of a chemical, occupational data could exaggerate the estimation of the sensitizing strength of a chemical to the consumer scenario. "Case histories" are studies typically on a single individual and are less helpful in providing information on sensitization in the general population. The suggested ranking would be:

- Validated clinical and diagnostic studies
- Epidemiological studies, with a preference for general population studies over occupational studies
- Well-conducted animal studies
- *In vitro* studies
- Cross-reactivity data
- Case histories

The panelists recommended the inclusion of QSARs, *in silico* data, and relative potency as additional considerations in the supplemental definition. While CSPC staff understands and agrees that QSARs and *in silico* data may be useful, staff plans to indicate that the utilization of these techniques would be as adjuncts to human and animal data and that these techniques, as noted in *footnote 24*, are not currently validated.

The CPSC staff draft proposed **revision of section** (*ii*) would read:

> *Strong.* In determining whether a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors, following a weight-of-evidence approach. Frequency of occurrence and range of severity of reactions in healthy or susceptible populations will be considered. The following factors (if available), ranked in descending order of importance, should be considered:
>
> - Validated clinical and diagnostic studies
> - Epidemiological studies, with a preference for general population studies over occupational studies
> - Well-conducted animal studies
> - *In vitro* test studies
> - Cross-reactivity data
> - Case histories
>
> Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, the threshold of human sensitivity, other data on potency and sensitizer bioavailability, if data is available. Bioavailability is the dose of the allergen available to interact with a tissue. It is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical. Utilization of QSARs and *in*

*silico* data are considered as adjuncts to human and animal data. Currently these techniques are not validated so their usefulness is limited.

**Supplemental Definitions -**
(iii) *Severity of reaction.*

*The minimal severity of a reaction for the purpose of designating a material as a "strong sensitizer" is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:*

- *physical discomfort*
- *distress*
- *hardship*
- *functional or structural impairment*

*These may, but not necessarily, require medical treatment or produce loss of functional activities.*

**Panel Discussion**
Some of the panelists believed that chronic morbidity and persistent clinical manifestations should be added to the list of qualifiers for "substantial illness". It was suggested by the panelists that an estimate of the relative potential for persistent morbidity could be derived from epidemiological studies and case reports.

As described in the discussion in section (*ii*) above, the panel recommended utilizing the ratings in the AMA's *Guides to the Evaluation of Permanent Impairment* for the determination of "severity of reaction".

**CPSC Staff Summary**
A suggestion was made by the panelists that chronic morbidity and persistent clinical manifestations should be added to the list of qualifiers for "substantial illness". CPSC staff agrees and will include this modification to the supplemental definitions in the CPSC staff draft proposed definitions.

As described in the discussion in section (*ii*) above, the panel recommended utilizing the ratings in the AMA's *Guides to the Evaluation of Permanent Impairment* for the determination of "severity of reaction". As discussed, CPSC staff would need to adjust the AMA severity classifications for application to the sensitizer definition. The revised classifications could be placed together in the form of separate guidelines for the determination of severity of response. CPSC staff believes that the examples provided in the definition to describe substantial illness (e.g., physical discomfort, distress), should remain in the definition since other

organ systems (e.g., ocular, oral) besides the respiratory and dermal systems are considered as locations for hypersensitivity. The guidelines developed for the respiratory system and skin may not be appropriate for these other organ systems.

CPSC staff believes that section (*iii*) is redundant with section (*ii*) which includes "*severity of reaction*" as a consideration within its definition for "*strong"*. The defining and qualifying sentences for "*severity of reaction*" could be incorporated into section (*ii)*.

CPSC staff will include in its draft proposed revision the consideration of the location of the hypersensitivity response. A severe hypersensitivity response to the face, hands or feet could have a significant impact on organ function (e.g., respiration) and quality of life. In emergency care, injuries to these body locations are given a priority one status for injury severity.

CPSC staff has prepared criteria for determining respiratory and skin severity (NAEPP guidelines[30] and W-AZS system[31]) which are found in Appendix C. These are a work in progress and staff will recommend their inclusion into CPSC's revised Chronic Hazard Guidelines.

The CPSC staff revision to section (*iii*) would be to delete section (*iii*) and to include the following definition for "severity of reaction" in section (*ii*) such that the CPSC staff's draft proposed **revision to section** (*ii*) would read:

> *Strong.* In determining that a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors, following a weight-of-evidence approach. The following factors (if available), ranked in descending order of importance, should be considered:
>
> - Validated clinical and diagnostic studies
> - Epidemiological studies, with a preference for general population studies over occupational studies
> - Well-conducted animal studies
> - *In vitro* test studies
> - Cross-reactivity data
> - Case histories

[30] NAEPP, National Asthma Education and Prevention Program, was initiated in March 1989 to address the growing problem of asthma in the United States. The NAEPP is administered and coordinated by NIH's National Heart, Lung, and Blood Institute (NHLBI).

[31] W-AZS is a severity scoring system for atopic dermatitis developed by W Silny et. al., Acta Dermatovenerol Croat 2005; 3(4):219-24.

Frequency of occurrence and range of severity of reactions in healthy or susceptible populations are to be considered in determining that a substance is a “strong” sensitizer. The minimal severity of a reaction for the purpose of designating a material as a “strong sensitizer” is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:

- Substantial physical discomfort and distress
- Substantial hardship
- Functional or structural impairment
- Chronic morbidity

A clinically important reaction would be considered one with loss of function and significant impact on quality of life. Consideration should be given to the location of the hypersensitivity response, such as the face, hands and feet as well as persistence of clinical manifestations.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, the threshold of human sensitivity, other data on potency and sensitizer bioavailability, if data is available. Bioavailability is the dose of the allergen available to interact with a tissue. It is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical. Utilization of QSARs and *in silico* data is considered as an adjunct to human and animal data. Currently these techniques are not validated so their usefulness is limited.

**Supplemental Definitions -**
(iv) *Significant potential for causing hypersensitivity.*

*“Significant potential for causing hypersensitivity” is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance, documented medical evidence of allergic reactions obtained from epidemiological surveys or individual case reports, controlled in vitro or in vivo experimental assays, or susceptibility profiles in normal or allergic subjects.*

**Panel Discussion**

The panelists suggested that animal studies and qualifiers for susceptibility profiles (e.g., genetics, age, gender, and atopy[32]) be added to the list of considerations.

There was discussion among the panel members regarding the term "normal" in the last phrase with a suggestion to replace it with either "naïve" or "non-sensitized".

**CPSC Staff Summary**

The panelists suggested that animal studies and qualifiers for susceptibility profiles (e.g., genetics, age, gender, and atopy) be added to the list of considerations. The term "*in vivo"* is considered by the general scientific community to include both human and animal studies. Therefore, it is unnecessary to specify "animal studies" since these studies are included in "*in vivo*" experimental studies.

There is a complex relationship between exposure to allergens, the development of allergic sensitization, and the onset and exacerbation of allergic diseases. Genetic factors have been shown to play a role in susceptibility to allergy and asthma. Parents with asthma have more than a 60% chance of having at least one child with asthma. Significant progress has recently been made in identifying genes responsible for susceptibility to allergic diseases. More than 35 genes (e.g., several variants of the IL-13 gene differentially promote mechanisms that lead to allergic inflammation) have been associated with asthma or related allergic diseases in multiple populations. However, none of these genes has been shown so far to contribute to risk in all populations studied.[33] The incidence of asthma has risen dramatically in the past 20 years, a period far too short to reflect any significant changes in the gene pool. This supports the important role that other susceptibility factors and the environment may have on the development of allergic diseases like asthma. The importance of age, gender, race and occupation in the development of allergies has been shown in many studies[34]. Therefore, CPSC staff will include the susceptibility qualifiers (e.g., genetics, age, gender, and atopic status) in the CSPC staff draft proposed supplemental definitions.

The panel members recommended replacing the term "normal" with either "naïve" or "non-sensitized". CSPC staff believes the term "non-sensitized" is preferable to "naïve"; "naïve" denotes that the individual is non-exposed. The term "non-sensitized" is the more appropriate term for what would be

[32] Atopy is a genetic predisposition to allergy and for producing IgE antibodies

[33] Ober C et. al., Curr Opin Immunol. 2005 Dec, 17(6):670-8; Osmola A et. al., Acta Dermatovenerol Croat 2005, 13(2):122-6. Hoffjan S et. al., J Mol Med 2005 Sep, 83(9):682-92.

[34] Wohrl S et. al., Pediatr Dermatol 2003, 20(2):119-23.

considered the control general population because it includes both non-exposed individuals and exposed individuals who are not sensitized to the allergen.

The CSPC staff draft proposed **revision to section** (*iv*)[35] would read:

> *Significant potential for causing hypersensitivity.* "Significant potential for causing hypersensitivity" is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance; documented medical evidence of allergic reactions upon subsequent exposure to the same substance obtained from epidemiological surveys or individual case reports; controlled *in vitro* or *in vivo* experimental studies; and, susceptibility profiles (e.g., genetics, age, gender, atopic status) in non-sensitized or allergic subjects.

**Supplemental Definitions -**
(v) *Normal living tissue.*

*The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory or gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion or inhalation.*

**Panel Discussion**
The panelists felt that this section was fine as written with the addition and consideration of the mucosal system, specifically highlighting ocular and oral systems.

**CPSC Staff Summary**
The panelists recommended consideration of other organ systems, including the mucosal system, specifically highlighting ocular and oral systems. CPSC staff agrees and will include this modification to the supplemental definitions in the CSPC staff draft proposed definitions.

As discussed in section (i), the panelists noted that in the future, with progress in the science, there may be a need to have a definition for each class of allergen (e.g., chemical, protein, respiratory, ocular and skin). This would be somewhat similar to the GHS definition which has separate definitions for respiratory and dermal (skin) sensitizers. However, the panelists did not make such a suggestion at this time since insufficient evidence exists to clearly separate the sensitization characteristics (e.g., different mechanisms of sensitization) of the different target organs.

[35] Section (iv) would become section (iii) with the deletion and incorporation of the original section (iii) into section (ii). Keeping in line with the emphasis of the statutory definition this paragraph will be moved to the beginning of section (ii).

The CPSC staff draft proposed **revision to section** (v)[36] would read:

> *Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory tract, gastrointestinal tract or mucosal system (e.g., ocular, oral), either singly or in combination, following sensitization by contact, ingestion or inhalation.

## B. Question #2

**The statutory definition has the classification of a sensitizer as that of a "strong sensitizer"; should additional classification categories (e.g., potency) be included as is being considered with the GHS? If so, please indicate the categories and supporting evidence for their establishment. If additional classifications are to be included, are the current classification guidance criteria sufficient (which are stated as "a clinically important reaction, produce substantial illness, including physical discomfort, distress, hardship, functional or structural impairment; which may, but not necessarily, require medical treatment or produce loss of functional activities")?**

Background

The GHS indicates that "*substances shall be classified as a respiratory sensitizer in accordance with the following criteria: if there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or if there are positive results from an appropriate animal test*." Similarly, the GHS shall classify substances as contact sensitizers "*if there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or, there are positive tests from an appropriate animal test.*" The GHS indicates that appropriate animal tests would include the guinea pig maximization test (GPMT), Buehler guinea pig test, and local lymph node assay (LLNA). The mouse ear swelling test (MEST) could be utilized as a first stage test in the assessment of skin sensitization potential (see Appendix D for a description of these tests).

The GHS indicates for skin sensitizers that "*for the purpose of hazard classification it may be preferable to distinguish between strong and moderate sensitizers. However, at present animal or other test systems to subcategorize sensitizers have not been validated and accepted. Therefore, sub-categorization should not yet be considered as part of the harmonized classification system*." Classification categories up to a 4-level scheme (weak, moderate, severe, extreme) for sensitizing strength

[36] Section (v) would become section (iv) with the deletion and incorporation of the original section (iii) into section (ii).

(potency) have been proposed by the OECD Expert Group. In one of the options, the classification categories are based solely on chemical concentration ranges which result in a 3-fold change in lymph node proliferation as determined by the LLNA (see CPSC staff summary below and Appendices A and D).

**Panel Discussion**

The panelists fell into two opposing groups in their responses to this question. The majority of the panelists felt that the guidance in the revised supplementary definitions is broad enough and that a weight of evidence approach is sufficient for the determination of sensitizing strength. This group also stated that the current range of studies and research using the LLNA are inadequate to recommend the use of the assay to classify sensitizers according to potency.

Some panelists even questioned the appropriateness of the LLNA since it only measures the induction stage of sensitization. They also questioned it because it does not reflect the range of variability in human exposure and response. A panelist suggested that some uncertainty factor may need to be considered to account for disparities between animal and human "predictive" test methods.

The remaining panel members stated that it is possible to categorize sensitizers according to a range of potency classes based on LLNA results; specifically into the four category scheme proposed to GHS by the OECD Expert Group (weak, moderate, severe, extreme). These panelists also suggested that the categorization of a sensitizer would be in addition to the other parameters included in section (*ii*) of CPSC's supplemental definition, and not as a replacement.

The panelists stated that if potency categories are included in the supplemental definitions, a discussion would be required of the criteria for each category with respect to the particular target organ (e.g., respiratory, dermal, oral, ocular).

Some panelists recommended that a more universal term for "strong" may be "relative potency".

One of the panelists suggested that the supplementary definitions include the notation that the frequency of allergy is a function of the nature and extent of allergen exposure, not just of allergen potency.

**CPSC Staff Summary**

The majority of the panelists felt that the guidance in the revised supplementary definitions is broad enough and that a weight of evidence approach is sufficient for the determination of whether a chemical is a

"strong sensitizer". This group also stated that the current range of studies and research using the LLNA is inadequate to recommend the use of the assay to classify sensitizers according to potency.

In 1997, the murine assay LLNA was proposed to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)[37] as a stand-alone alternative method to the Guinea Pig Maximization Test (GPMT) and the Buehler Assay (BA) for hazard identification. ICCVAM carried out an independent scientific peer review of the validation status of the LLNA for assessing the potential for allergic contact dermatitis by chemical exposure. In the ICCVAM 1999 report, the consensus of the peer review panel was that the LLNA performed as well as the GPMT and BA for hazard identification of strong to moderate chemical sensitizing [dermal] agents but lacked strength in accurately predicting some weak sensitizers and some strong irritants. The potency of standard allergens was minimally evaluated.

Recently, the LLNA has been proposed as a technique to measure the relative potency of a contact allergen based upon $EC_3$ values. An $EC_3$ value is an estimated concentration of chemical necessary to elicit a 3-fold increase in lymph node cell proliferative activity. This 3-fold increase is used to discriminate between sensitizers and non-sensitizers; however, the use of LLNA ($EC_3$ values) has not been validated for the determination of relative potency.

Historically, the GPMT and the BA are the primary animal assays that have been used to determine the sensitizing ability of a chemical. These assays have been modified to determine potency. Experimental animal data and human data can be utilized for determining sensitizing strength. One approach by a panel of German experts ranked 244 substances into three categories based on potency[38]. Categorization was determined by a weight-of-evidence approach using human clinical data, patch test results and animal data, when available. Consideration was given to prevalence, strength of sensitization in animals and humans, severity of response and cross-reactivity to known sensitizers. The three categories were Category A - significant allergen, Category B - solid-based indication for contact allergenic effects, and Category C - insignificant contact allergen (or questionable contact allergenic effect).

[37] The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was established in 1997 by the National Institute of Environmental Health Sciences (NIEHS); Public Law 106-545, ICCVAM Authorization Act of 2000, established ICCVAM as a permanent committee. The Committee is composed of representatives from 15 Federal regulatory and research agencies; these agencies generate, use, or provide information from toxicity test methods for risk assessment purposes. The Committee coordinates cross-agency issues relating to development, validation, acceptance, and national/international harmonization of toxicological test methods.

[38] Schlede E et.al., Toxicology 2003; 193(3):219-59.

Current criticism among the scientific community for the EU-proposed four potency category scheme based on $EC_3$ values is that there is insufficient distinction between the potency categories.

Some panelists recommended that a more universal term for "strong" may be "relative potency". CPSC staff disagrees with this suggestion of replacing "strong" since it would require changing the statutory definition in addition to the supplemental definition. Furthermore, "relative potency" is a general term which provides no indication of sensitizing strength and thus the number of chemicals declared as sensitizers would be vastly increased, as would the number of products that would require labeling. The intent of the FHSA is to address only a subset of sensitizers, those having a significant health impact.

In summary, CPSC staff agrees that the supplemental definition is broad enough and that a weight of evidence approach should be used to determine whether a chemical is a "strong sensitizer". CPSC staff believes that the LLNA is inadequate as a stand-alone for determining the sensitizing strength of a chemical, particularly since the assay has not been validated for the determination of potency. No additional classifications based on potency are recommended.

## C. Question #3

**Immunotoxicology[39] continues to be a dynamic field. Should specific testing/data be specified for the determination of the sensitizing ability of a chemical? If so, what validated testing?**

Background information provided to the panel:
See Appendix D

**Panel Discussion**

Much of the discussion in relationship to Question #1 is applicable and overlaps with this question, particularly that a weight of evidence approach should be used to determine whether a chemical is a "strong sensitizer". Panel members who either developed the assay or who have utilized the LLNA, considered it a well validated test for most chemical classes that produce allergic contact dermatitis. Some panelists stated that the GPMT, while sensitive, is not as encompassing as the LLNA. However, the aforementioned caveats in Question #2 and Appendix D for the LLNA (e.g., exposure conditions, genetics, low molecular weight chemicals, and

[39] Immunotoxicology is a subsection of toxicology that deals with the effects of toxic substances on the immune system. Adverse effects include chemically-induced immunosuppression (which may be manifested as either decreased resistance to opportunistic infections or increased susceptibility to cancer) and immunostimulation (which can result in hypersensitivity reactions and increased risk of autoimmune diseases).

negative control responses) were considered by the majority of the panelists as factors weakening its predictive value for human responses to all chemical classes of allergens. Some panelists stated that although there is no validated test for respiratory allergens, the LLNA has been shown to give positive responses for some sensitizing chemicals in this class; whether this is true for all respiratory sensitizers is currently unknown.

Some of the panelists indicated that the mouse intranasal test (MINT) has been shown to be a good tool for identifying protein allergens; however, along with the new approach of "cytokine profiling", it has not been validated for predictive use. These assays are still in the developmental stage.

Some of the panelists indicated that large inter-laboratory variability with the mouse IgE test diminishes its applicability for use in classification and identification of sensitizers. This assay is also limited to assessing just IgE-mediated allergens[40].

There was general agreement among the panelists that the determination of sensitizing potential should be a weight of evidence approach.

**CPSC Staff Summary**

New data and methodologies continue to be developed; therefore to specify particular assays would likely result in their replacement as new data and information become available. CPSC staff believes that the determination of sensitizing potential should be a weight of evidence approach, utilizing all available validated tools and data. This approach is in line with the CPSC's Chronic Hazard Guidelines in the determination of "sufficient evidence" of carcinogenicity which requires that a substance has been tested in well-designed and well-conducted studies. Examples of well-designed and well-conducted carcinogenicity studies are indicated as studies conducted by the National Toxicology Program (NTP) or studies that follow Office of Science and Technology Assessment and Policy (OSTP) guidelines.

## D. Question #4

**Recognizing the differences between the mature and the developing immune systems, are there differences in susceptibility to sensitization between children and adults? If so, how should, or can this, at this time be addressed in the risk assessment process? Are**

[40] Allergens cause an allergic response via other antibodies such as IgG or through T lymphocyte-mediated processes.

**there other susceptible populations that should be taken into consideration? Infants and children have a larger volume of distribution, larger surface area to body weight ratio. The current method of assessing skin threshold dose for sensitization is concentration per square unit skin. Is this appropriate for children? It has been suggested that dermal exposure to chemicals (e.g., polyurethane and isocyanates in the footnoted reference) could occur early in life through contact with consumer products and medical materials[41]. Free isocyanate was detected in these products at levels that were considered sufficient to produce dermatological reactions in patients. It was suggested that the skin of human neonates is thin, delicate and susceptible to alterations in integrity, and thus serves as a poor barrier in comparison to the skin of older children and adults thereby creating opportunities for dermal exposures and predisposing children to hypersensitivities. Is this an accurate assessment and an area of concern for sensitizing substances? With the available current information, are there differences between respiratory sensitizers and contact sensitizers when determining children's susceptibility?**

Background information

Background information, detailed in the following paragraph, was included in order to solicit comments from the panel on some of the recent data on children's potential for enhanced susceptibility to sensitization. This is because in the past, the overriding dogma had been that sensitization is a process that occurs over a length of time and that a latency period exists between the initial exposure(s) (induction) and exhibition of clinical signs (elicitation). Furthermore, the common perception was that, in general, children were not more susceptible to sensitization than adults. CPSC staff was particularly interested in the panel addressing the comparability of young children (e.g., neonates, infants) to older children and adults. The discussion regarding this question (#4) could be relevant for the staff's risk assessment of sensitization once a hazard identification of "strong sensitizer" has been made by the Commission.

Background information provided to the panel

Asthma is the most common chronic disease of children and is phenotypically a heterogeneous disorder. Over the past several years, four clinical asthma phenotypes have been well defined in children: non-wheezers, transient early wheezing (first 3 years only), persistent wheezing/asthma (atopic and non-atopic) and late-onset wheezing (only after 3 years). These phenotypes are based on the findings of the longitudinal Tucson Children's Respiratory Study (TCRS) and are supported by findings from the German Multicenter Allergy Study, a New Zealand longitudinal study, and the Melbourne Epidemiological Study of

[41] Kronce CA et. al., Med Sci Monit 2003; 9(12):HY39-43.

Childhood Asthma[42]. These longitudinal studies followed large randomly selected cohorts of children from birth to adult life. One of the most important findings of the TCRS was that events occurring early in life appear to be important determinants of subsequent asthma. Elevated IgE levels near the end of the first year of life were associated with later persistent wheezing (at 6 years of age and older) and asthma. It appeared that the children destined to develop persistent wheezing were already "programmed" immunologically, before the first lower respiratory infection, to respond differently to an infection. The slopes of the change in lower lung function measurements (for 5 year periods up to age 16 for the TCRS, and for 7 year periods up to age 35 for the Melbourne study) were similar for each of the aforementioned phenotypic groups, indicating that impairment of lung function occurred in early childhood; only the transient wheezers presented with lower lung function early in life before any respiratory insult.

At 6 years of age, persistent wheezers had the lowest lung function of any group. The decline of lung function may result from recurrent or ongoing airway damage during this period of rapid lung growth. This significant difference in having the lowest lung function was still detected at 11 years of age. The persistent wheezers showed the highest levels of IgE at the ages of 6 and 11.

The deficits in lung function in wheezing children were not significantly present shortly after birth, but seem to be acquired during the first years of life. As demonstrated in the Melbourne study, subjects with asthma and severe asthma at 7 years of age experienced abnormal pulmonary function as adults. These longitudinal studies support the contention that early initiation of symptoms and perhaps early allergic sensitization during the first 3 years of life may be very important risk factors for more severe disease and for significantly higher deficits in lung function.

**Panel Discussion**

The majority of the panel members concluded that children are at increased risk for sensitization. However, some of the panelists indicated that this may be based upon controversial epidemiological studies. Both panel members with clinical backgrounds strongly stated that children, even more so for children of atopic parents, have increased susceptibility to allergens[43]. Large cohort studies on aeroallergens were provided by some of the panelists as evidence of the increased susceptibility of

[42] Morgan WJ et. al., Am J Respir Crit Care Med 2005, 172:1253-8; Stein RT et. al., Paediatric Respiratory Reviews 2004, 5:155-61; Taussig LM et. al., JACI 2003, 111:661-75; Martinez FD, Pediatrics 2002, 109(2):362-7; Martinez FD, Paediatric Respiratory Reviews 2002, 3:193-7; Lau S et. al., Eur Respir J 2003, 21:834-41; Sears MR et. al., NEJM 2003, 349(15):1414-22; Horak E et. al., BMJ 2003, 326(7386):422-3; Phelan PD et. al., JACI 2002, 109:189-94.

[43] Atopy is a genetic predisposition to allergy and for producing IgE antibodies. Reports in published literature indicate that at least 20% to 40% of the general population is atopic.

children[44]. In one study, 18% of the infants (mean age was 13.7 months) born to atopic parents exhibited a positive skin prick test to at least one common aeroallergen. Some of the panelists agreed with the background information provided by CPSC staff, adding that the origins of asthma appear to be in infancy or even pre-natal exposure, although more research is needed for determination of its root causes.

The panelists with clinical backgrounds stated that atopic status is an important susceptibility factor for the development of allergic skin and respiratory sensitization to protein allergens. An example provided by one panelist indicated that abundant evidence exists showing that exposed atopic adult workers are at a much greater risk for IgE-mediated sensitization than their non-atopic similarly exposed co-workers. The panelists stated that epidemiologic studies indicate that T-helper 2 lymphocyte (T helper type 2 cells [Th2], see Appendix A) driven development of atopy (defined by skin prick testing) is determined early in life and unlikely to be initiated after age 16.

A 2001 National Health and Nutrition Examination Study (NHANES) III report[45] was of greater concern to the panelists. The report demonstrated that 52% of the children between the ages of 6 and 17 exhibited at least one positive skin prick test from a panel of 10 aeroallergens. The panelists believe that this and other evidence reflects a higher prevalence of atopy in young versus adult populations in the US and other developed countries. The panelists indicated that this rise in atopy prevalence is a phenomenon, noted over the past three decades, that has paralleled a dramatic increase in incidence rates of asthma and allergic rhinitis. It is likely that in the future effects in an atopic population will reflect the majority of the population at large.

During the July 2005 meeting the panelists indicated that differences may exist between susceptibility for respiratory allergens and dermal allergens with respect to the age of the individual, such that neonates/infants may have increased susceptibility to respiratory allergens, but potentially not to contact allergens.

Panel members disagreed with regard to whether children exhibit enhanced susceptibility to skin allergens. The clinician panel members stated that significant toxicity, even death, in neonates has been observed with some topical drugs and chemicals. The clinician panelists stated that neonates are more susceptible to percutaneous absorption (while another

[44] Kimata et. al., Public Health 2005 Dec, 119(12):1145-9; Becker AW et. al., JACI 2004, 113(4):650-6; Ryan PH et. al., JACI 2005, 116(2):279-84; Sandin A et. al., Pediatr Allergy Immunol 2004, 15(4):316-22; Guillet MH et. al., Ann Dermatol Venereol 2004, 131(1Pt1):35-7; Meglio P et. al., J Investig Clin Immunol 2002, 12(4):250-6.
[45] von Mutius E et. al., Thorax 2001, 56(11):835-8.

panel member stated that he was not aware of differences in skin properties between neonates, infants and adults). The panelists who believe there is no increased sensitivity in children with regards to skin sensitizing substances, stated that reactivity to 2,4-dinitrochlorobenzene (DNCB)[46] has been shown to be low in infants, and allergic dermatitis to poison ivy-oleorisin is rarely seen in early life. However, other panelists stated that there is some data indicating the potential hypersensitivity of children to protein allergens. A recent controlled experiment cited by a panelist suggests that atopic children are more susceptible to natural rubber latex sensitization than are non-atopic children. Therefore the consensus from the July discussions was that for skin allergens, enhanced susceptibility for young children may be chemical specific.

**CPSC Staff Summary**

The majority of the panel members concluded that children are at increased risk for sensitization especially from respiratory allergens, but some of the panelists indicated that this conclusion may be based upon controversial epidemiological studies. Some of the panelists agreed with the background information, adding that the origins of asthma appear to be in infancy or even pre-natal exposure, although more research is needed for determination of its root causes. Recent data on the developing immune system has demonstrated a T-helper-2 (Th2; see Appendix A) biased system in newborns and infants, which could establish a pro-active state for respiratory allergens.

Large cohort studies on aeroallergens were provided by the panelists as evidence of increased susceptibility of children. However, these studies did not compare children to adults. The studies mainly focused upon children that were atopic or non-atopic. One study demonstrated a greater than five-fold factor increase in reactivity to challenge among atopic children compared to non-atopic children. An extraordinary rise in atopy has paralleled the dramatic increases in the rates of asthma and allergic rhinitis. One panelist stated that physicians believe that, in the future, atopic individuals may reflect the majority of the population at large. The number of asthma cases in the US for all age groups has increased by at least 75% over the past two decades, while the rate among children under the age of 5 has increased over 160%[47]. Numerous recent studies, including the NHANES III study provided by a panelist, demonstrate a higher prevalence of atopy in young versus adult populations in the US.

The linkage between increases in both allergic disease and atopy, may apply for respiratory allergens but not other organ systems associated with hypersensitivity responses (e.g., skin, gastrointestinal, ocular). At

[46] DNCB is the chemical most often used in studying the mechanism of allergic contact hypersensitivity.
[47] Centers for Disease Control and Prevention (CDC), April 24, 1998. "*Surveillance for Asthma – United States, 1960-1995*." MMWR Surveillance Summaries 47(SS-1):1-28.

present, CPSC staff believes there may be insufficient data to make this distinction.

The route of exposure is a separate entity and not a consideration with relation to susceptibility other than it can create more opportunity for exposure. Individuals can be sensitized to respiratory allergens solely via dermal exposure, however the reverse has not been definitively shown. The development of sensitization and predisposition to sensitization is a subject of active research. Current studies have demonstrated a complex process of interaction among the innate immune system, the adaptive immune system (of which atopy is one component) and the properties of the allergen. The interplay of these systems has been shown to impact the sensitizing potential of an allergen[48]. Whether this interplay is applicable to all allergens (e.g., respiratory, dermal, oral) is currently unknown.

Differences may exist between susceptibility to respiratory allergens and dermal allergens such that neonates/infants may have increased susceptibility to respiratory allergens but potentially not to skin allergens. However, neonatal infants have acquired allergic contact dermatitis from vinyl identification bands, nickel, neomycin, ethlenediamine, thimerosal, merbromlin (mercurochrome), balsam of Peru, rubber chemicals in shoes and poison ivy[49]. The authors also state that dermatitis due to apparel (especially wool) and to sensitizers in shoes is frequent; and allergic dermatitis to poison ivy oleoresin and certain topical medications is not rare in early life[49]. More research is necessary to determine whether these differences between types of allergens exist.

The panelists disagreed with respect to enhanced susceptibility of children to skin allergens. Examples were provided by the panelists indicating enhanced or diminished sensitization of children to contact sensitizers which might suggest that enhanced susceptibility of young children to skin sensitizers may be chemical specific.

In conclusion, the consensus of the panel members was that children are at increased risk for sensitization, particularly to respiratory sensitizers. Currently, there is conflicting data to determine age specific susceptibility to skin allergens; however, this may change as more information becomes available since recent publications indicate that allergic dermatitis is the most common skin condition in children under the age of 11 years. In addition, the percentage of children diagnosed with allergic dermatitis has

[48] Van Woerden H. Med Hypotheses 2004, 63(2):193-7; Almqvist C et. al., Clin Exp Allergy 2003, 33(9):1190-7; Ritz BR et al, Allergy 2002, 57(4):357-61.
[49] Fisher's Contact Dermatitis, 2001, 5th edition, Rietschel RL and Fowler J, eds. Lippincott, Williams and Wilkins, New York.

increased more than 300% since the 1960's[50]. CPSC staff believes that children should be considered to be at increased risk to respiratory sensitizers and that skin sensitizers should be evaluated on a case-by-case basis when estimating potential risks associated with exposures to substances that are considered to be "strong sensitizers".

## E. Question #5

**Many consumer products will commonly have sensitizing substances present in mixtures. Surfactants can aid in the penetration of sensitizing chemicals via their disruption of the skin barrier. It is hypothesized that depending upon the allergen, the surfactant may act synergistically (e.g., nickel with sodium lauryl sulfate [SLS], methyldibromoglutaronitrile with SLS) in the allergic response and therefore alter the determination of threshold values and the risk for elicitation of allergic contact dermatitis. Is this accurate? Is this type of synergistic response prevalent enough that this information should be considered within the FHSA definition of a sensitizer?**

**Panel Discussion**

Some panel members felt this question was out of their area of expertise, although all were in agreement that surfactants can act directly as irritants particularly in susceptible individuals. However, for non-sensitizing irritants, one panel member stated that based upon current case studies, synergism between surfactants and an irritant chemical in causing sensitization is not prevalent.

There was no agreement by the panelists on the ability of surfactants, particularly SLS, to enhance the risk of sensitization. A panelist indicated that the utilization of surfactants in human and animal experimental sensitizing studies has led to the development of the "Danger Hypothesis", which states that it is necessary for tissue trauma to occur in order to initiate the process for a clinical dermal response.

One panelist mentioned the concept of "compound allergy", when the response is to the mixture itself and not the individual component chemicals. The frequency of occurrence of this "compound" response is unknown.

Some of the panel members stated that the consideration of matrix effects, or complexity of a mixture, may be more appropriate for the risk assessment process rather than in the hazard identification process, and

[50] American Academy of Allergy Asthma and Immunology (AAAAI), Allergy Statistics, Media Kit; and, Horan RF et. al., JAMA 1992, 268:2858-68.

therefore should not be considered for inclusion in the "strong sensitizer" supplementary definition.

**CPSC Staff Summary**

There was no agreement by the panelists on the ability of surfactants, particularly SLS, to enhance the risk of sensitization. Surfactants have been shown experimentally to aid in the development of allergic contact dermatitis by priming the exposed individual via an inflammatory response. The guinea pig (GPMT) and human maximization studies are directly based upon this fact, with SLS used to increase the sensitivity of the assays. As a panelist indicated, this has led to the development of the "Danger Hypothesis" which states that it is necessary for tissue trauma to occur in order to initiate the process leading to a clinical dermal response. This hypothesis is also under consideration for respiratory sensitizers.

The determination of the sensitizing capability of a chemical in a consumer product can be complex. Most human and animal experimental studies will assess a chemical for its sensitizing potential based on the pure chemical form. However, the exposure of the general population to a sensitizer in a consumer product is most likely to be to the chemical in the form of a mixture. The effect of the matrix (the mixture or formulation in which the chemical is present in the consumer product) can be pronounced, affecting both the bioavailability and the immunological activity of the potentially sensitizing ingredient.

Multi-fold increases in sensitization due to the presence of enzymatic activity from mixture components have been clearly demonstrated in detergent studies. Sensitizing potency for the chemical dihydroquinone was shown to vary by at least 20-fold between two different formulations.[51] Furthermore, clinical elicitation of contact allergy has been shown to be enhanced when more than one contact allergen is present. "Compound allergy", as stated by one panelist, can occur to the mixture itself and not the individual component chemicals, although the frequency of occurrence for this response is unknown.

Once a hazard identification of "strong sensitizer" has been made by the Commission, CPSC staff believes that consideration of matrix effects is important in the risk characterization. Consideration of the complexity of a mixture is important since the predominant exposure of the general population to sensitizers in consumer products will be in the form of mixtures and not the "pure" compound. This is similar to the FDA approach for sensitization testing for investigational new drugs which

[51] Lea LJ et. al., Am J Contact Dermat 1999 Dec, 10(4):213-8.

includes testing the entire formulation as well as the drug vehicle for sensitizing potential.[52]

## IV. **Overall CPSC Staff Summary with Rationale**

A scientific panel was convened by CPSC staff to address the definition of *Sensitization* which appears in section 2(k) of the Federal Hazardous Substances Act (restated in 16 CFR 1500.3(b)(9)) and supplemented in section 1500.3(c)(5). The statutory definition and amendments had not been reviewed since 1986 and the state of the science has advanced since then. The panel was comprised of six scientists from Federal agencies, academia and industry, each with regulatory, research and/or clinical experience with chemical and protein sensitizing agents. The objective of the panel was to examine the available information concerning sensitizers and, if appropriate, propose revisions to the existing FHSA definition for sensitization based on their knowledge as scientific experts in this field. In addition, the panel was to make suggestions regarding (1) classification criteria for a sensitizer, taking into account the GHS definition of sensitizers, (2) what testing/data CPSC should accept for the determination of sensitizing ability, and (3) the process for identifying a chemical as a sensitizer, particularly with regard to differences between children and adults and the existence of threshold responses in those populations.

Question 1, Supplemental Definition of Sensitizer

All panel members recommended that the FHSA definition be revised. They recommended the use of clear terminology when referring to the allergenicity associated with a chemical.

The panelists did not recommend modifications of the FHSA definition of "strong sensitizer" in order to harmonize with the GHS definitions of respiratory and skin sensitizers. The panelists believed that the FHSA definition is more comprehensive than the GHS definitions. The FHSA requires risk-based labeling (i.e., exposure and the resultant risk are required to make a determination whether a product containing a strong sensitizer would need to be labeled). A determination made under the FHSA would be compatible with the option for risk-based decision making in the GHS.

CPSC staff recommends that modifications be made to each supplemental definition section. The CSPC staff draft proposed revisions are summarized below.

*(i)* *sensitizer:* In this section the language will be simplified and the sentence "*Occasionally, a sensitizer will induce and elicit an allergic*

[52] This approach of testing the mixture is in contrast to that being used by the GHS. The GHS identifies a substance as a sensitizer and then sets a cut-off concentration level (e.g. ≥ 0.1% or ≥ 1.0% for skin sensitizers) at or above which a mixture needs to be classified and labeled.

*response on first exposure by virtue of active sensitization"* will be deleted.

*(ii)* *strong*: In this section:

- The language will be simplified.
- Definitions will be provided for some of the qualifiers (e.g., bioavailability).
- Terms will be deleted due to redundancy (e.g., *in vivo*) and lack of contribution to the definition (e.g., quantitative and qualitative risk assessment).
- A weight of evidence approach will be included for the determination of the strength of a sensitizer.
- Considerations for the use of QSARs and *in silico* data will be added along with the caveat that utilization of these techniques would be as adjuncts to human and animal data and that these techniques are not currently validated.
- The remaining qualifying factors will be ranked in order of importance, based on precedence for human data over animal data.

It was requested that more specific and, if available, more precise qualifications be provided for what designates a sensitizer as "strong". It was suggested by several panelists that the AMA's *Guides to the Evaluation of Permanent Impairment* be used to provide objective criteria for evaluating the severity of a reaction in the respiratory system and skin. CSPC staff recommends consideration of the AMA and other similar guidelines in the development of guidelines assessing whether a sensitizer meets the definition of "strong".

*(iii)* *Severity of reaction*: This section, redundant with "severity of reaction" in section (*ii) strong,* will be moved and included in section (*ii) strong*.

*(iv)* *Significant potential for causing hypersensitivity*: In this section, qualifiers for susceptibility profiles (e.g., genetics, age, gender, and atopic status) will be added to the list of considerations. The term "normal" will be replaced with "non-sensitized" to more accurately reflect what would be considered the general control population. This section will be moved to the beginning of section (ii).

*(v)* *Normal living tissue*: In this section consideration of the mucosal system, specifically highlighting ocular and oral systems, will be added.

Question 2

The panelists were asked to consider whether additional classification categories (e.g., potency) other than "strong" should be included in the supplemental definition. The Local Lymph Node Assay (LLNA) was the primary focus of the discussion since the OECD Expert Group has proposed a 4-level scheme (weak, moderate, severe, extreme) for classifying sensitizing strength (potency) based solely upon LLNA $EC_3$ values to the GHS.

CPSC staff agrees with the majority of the panelists that the CPSC staff proposed revision of the supplemental definition is broad enough and that a weight-of-evidence approach is sufficient for determining the sensitizing strength of a substance. The group of panelists also stated that the current range of studies and research using the LLNA is inadequate to recommend the use of the assay to classify sensitizers according to potency. CPSC staff believes that the LLNA is inadequate as a stand-alone for determining the sensitizing strength of a chemical particularly since the assay has not been validated for the determination of potency. No additional classifications based on potency are recommended.

Question 3

The panelists were asked to consider whether specific testing should be specified for the determination of the sensitizing ability of a substance. Assays provided for them to consider included the Guinea Pig Maximization Test (GPMT), the Buehler Assay (BA), the Local Lymph Node Assay (LLNA), the mouse IgE test, "cytokine profiling" and the mouse intranasal test (MINT). Panelists noted strengths and weaknesses with each of the assays. However with the focus on the LLNA, the caveats for the LLNA (exposure conditions, genetics, low molecular weight chemicals, and negative control responses) were considered by the majority of the panelists as factors weakening its predictive value for human responses to all chemical classes of allergens.

CPSC staff agrees with the panelists that the determination of risk should be a weight of evidence approach, utilizing all available validated tools. New data and methodologies continue to be developed; therefore to specify particular assays would likely result in their replacement as new data and information become available. CPSC staff also agrees with the panelists that the LLNA, because of its lack of predictive value for human responses to all chemical classes, is not sufficient to satisfy all testing needs.

Question 4

The panelists were asked to consider children's potential for enhanced susceptibility to sensitization. The consensus of the panel members was that children are at increased risk for sensitization, particularly to respiratory sensitizers. Currently, there is conflicting data to determine age-specific susceptibility to skin allergens; however, this may change as more information becomes available. CPSC staff believes during the risk characterization step

that children should be considered at increased risk to respiratory sensitizers and that skin sensitizers should be evaluated on a case-by-case basis.

Question 5

The panelists were asked to consider matrix effects, or the complexity of chemicals in a mixture, since many consumer products will commonly have sensitizing substances present in mixtures. Some of the panel members stated that the consideration of matrix effects, or the complexity of a mixture, may be more appropriate for the risk assessment process rather than in the hazard identification process, and therefore should not be considered for inclusion in the definition. Once a hazard identification of "strong sensitizer" has been made by the Commission, CPSC staff believes that consideration of matrix effects is important in the risk characterization of a strong sensitizing chemical. Consideration of the complexity of a mixture is important since the predominant exposure of the general population to sensitizers in consumer products will be in the form of mixtures and not the "pure" compound. The Commission makes a decision on declaring the chemical as a strong sensitizer, but the form and risk characterization (e.g. label, no label or ban) is based on the product as a whole. Risk characterization and risk management would have to take into consideration the form in which the sensitizer is present in the actual product.

## V. **CPSC Staff Draft Proposed Supplemental Definition**

Based upon suggestions of the scientific panel and input from CPSC staff, the following draft supplemental definition is proposed by CPSC staff[*].

> *Sensitizer.* A sensitizer is a substance that will induce a state of immunologically-mediated hypersensitivity (including allergic photosensitivity) following a variable period of exposure to that substance. Hypersensitivity to a substance will become evident by an allergic reaction elicited upon re-exposure to the same substance.
>
> *Significant potential for causing hypersensitivity.* Before designating any substance as a "strong sensitizer", the Commission shall find that the substance has significant potential for causing hypersensitivity. *Significant potential for causing hypersensitivity* is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance; documented medical evidence of allergic reactions upon subsequent exposure to the same substance obtained from epidemiological surveys or individual case reports; controlled *in vitro* or *in vivo* experimental studies; and, susceptibility profiles (e.g., genetics, age, gender, atopic status) in non-sensitized or allergic subjects.

[*] Section designations (e.g., "i") have been removed from the proposed supplemental definition

In determining whether a substance is a “strong” sensitizer, the Commission shall consider the available data for a number of factors, following a weight-of-evidence approach. The following factors (if available), ranked in descending order of importance, should be considered:

- Validated clinical and diagnostic studies
- Epidemiological studies, with a preference for general population studies over occupational studies
- Well-conducted animal studies
- *In vitro* test studies
- Cross-reactivity data
- Case histories

Before the Commission designates any substance as a “strong” sensitizer, *frequency of occurrence and range of severity of reactions* in healthy or susceptible populations will be considered. The minimal severity of a reaction for the purpose of designating a material as a “strong sensitizer” is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:

- Substantial physical discomfort and distress
- Substantial hardship
- Functional or structural impairment
- Chronic morbidity

A clinically important reaction would be considered one with loss of function and significant impact on quality of life. Consideration should be given to the location of the hypersensitivity response, such as the face, hands and feet as well as persistence of clinical manifestations.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, the threshold of human sensitivity, other data on potency and sensitizer bioavailability, if data is available. Bioavailability is the dose of the allergen available to interact with a tissue. It is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical. Utilization of QSARs and *in silico* data is considered as an adjunct to human and animal data. Currently these techniques are not validated so their usefulness is limited.

*Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory tract, gastrointestinal tract or mucosal system (e.g., ocular,

oral), either singly or in combination, following sensitization by contact, ingestion or inhalation.

For a product containing a strong sensitizer to be designated a hazardous substance and to require cautionary labeling under the FHSA[53], the product must be capable of causing substantial personal injury or substantial illness during or as a result of customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children.[54] This requires consideration of the route and the level of exposure that can be expected to be presented by the strong sensitizer as it exists in the particular substance. Therefore, the determination of whether a cautionary label is required must be made on a product-by-product basis and is not solely based upon the presence of a strong sensitizer in a product. If a substance containing a strong sensitizer is determined to be a hazardous substance under the FHSA, cautionary labeling, including the signal words "Caution" or "Warning" and an affirmative statement of the hazard could be required (e.g., "may produce allergic reaction by skin contact or if inhaled"). While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic hazards, the manufacturer is required to label a product appropriately according to the FHSA requirements. However, if a toy or other article intended for use by children is a hazardous substance or bears or contains a hazardous substance in such a manner as to be susceptible to access by a child to whom such toy or other article is entrusted, then the product is by definition a "banned hazardous substance" unless specifically exempted by regulation.[55]

## VI. **Conclusions**

Currently, the regulation of strong sensitizers under the FHSA is complex. Staff believes that its draft proposed revisions to the supplemental definition of "strong sensitizer" will help clarify the definition and aid manufacturers in making the determination as to whether labeling is necessary and appropriate. At this time, the Commission would have to designate a substance as a "strong sensitizer" before labeling could be required.

[53]The FHSA, at 15 U.S.C. 1261(p), requires cautionary labeling for any article intended or packaged for household use if it contains a hazardous substance.
[54]15 U.S.C. §1261(f)(1)(A)
[55]15 U.S.C. §1261(q)(1)(A)

# Appendix A
# Hypersensitivity and Sensitization

Hypersensitivity or allergy results when the immune system responds to a specific allergen in an exaggerated or inappropriate manner. These reactions have been divided into four types by Coombs and Gell[56] (Types I, II, III and IV), representing four different mechanisms leading to the body's response to the allergens. One characteristic common to all four types of hypersensitivity reactions is the necessity of prior exposure leading to sensitization in order to elicit a reaction upon subsequent exposure. In general, substances which are stronger sensitizers require lower doses over a shorter exposure period in order to sensitize, while weaker sensitizers require higher doses over a longer exposure period.

For hypersensitivity Types I, II and III, exposure to an antigen results in the production of a specific antibody (IgE, IgG or IgM). Allergic reactions of the airways, skin or mucous membranes as a result of exposure to allergenic substances are commonly associated with two immune mechanisms: the immediate hypersensitivity (Type I) response which normally occurs within minutes of exposure in a previously sensitized individual and the delayed hypersensitivity (Type IV) response which occurs 24 to 72 hours following exposure (also to a previously sensitized individual).

Sensitization occurs as the result of exposure to allergens typically through the respiratory tract, skin, or the gastrointestinal tract (research into ocular sensitization is ongoing). The Type I reaction (e.g., contact urticaria, rhinitis, asthma, anaphylaxis) is primarily mediated by immunoglobulin E (IgE) antibodies bound to mast cells and basophils formed during sensitization (also known as the induction phase) and released into the systemic circulation. Upon re-exposure to the allergen (the elicitation phase), the allergen binds to its specific IgE antibodies which are already bound to mast cells. This interaction of allergen and IgE antibodies causes the mast cells to release a variety of substances (e.g., histamine, heparin, prostaglandins, leukotrienes) including cytokines typically from the T-helper 2 (Th2) type cells. Th2 cells are a subset of T lymphocytes which produce cytokines such as interleukin 4 (IL-4), IL-5, IL-9 and IL-13. These T cells and their products have been shown to be implicated in asthma and other airway diseases. In a Type I reaction the skin and respiratory tracts may respond after dermal exposure to the causative agents. At this time, skin sensitization after inhalation exposure has not been clearly demonstrated.

The Type IV reaction is a T-cell mediated immune response that requires a step-wise series of cellular events occurring within the body (the induction phase) leading up to the inflammatory response (the elicitation phase) upon re-exposure. The induction phase typically involves the association of allergens (haptens) with carrier proteins, presentation of the protein-hapten conjugates to the regional lymph nodes (via antigen presenting cells such as dendritic cells and Langerhans cells), recognition of the

[56] *Casarett & Doull's Toxicology, the Basic Science of Poisons*, Sixth Edition, CD Klaassen, editor; McGraw-Hill, New York, 2001.

conjugates by specific T cells, and proliferation of the specific T cells in draining lymph nodes. The local lymph node assay (LLNA) is an *in situ* test that capitalizes on this lymphoproliferation. The most common Type IV reaction is allergic contact dermatitis.

Photoallergy is a special case of type IV hypersensitivity in which UV radiation (either as natural sunlight or artificial light) causes changes to the structure of a substance. This altered substance then follows the sensitization path as described above for type IV sensitizers. The allergic response (commonly a rash with itching, redness, and blisters) is typically confined to the light exposed areas.

# Appendix B
# AMA Guides to the Evaluation of Permanent Impairment[57]

## Respiratory system

The American Medical Association (AMA) utilized the American Thoracic Society (ATS) guidelines to revise its previous versions of asthma impairment criteria. The ATS considers an "adverse" respiratory health effect to be a medically significant physiologic or pathologic change as evidenced by one or more of the following: (1) interference with normal activity of the affected person (2) episodic respiratory illness (3) incapacitating illness (4) permanent respiratory injury, and/or (5) progressive respiratory dysfunction. The ATS adds a caveat that small, transient reductions in pulmonary function should not necessarily be regarded as adverse; however reversible loss of function in conjunction with symptoms, or permanent loss of function, should be considered adverse.

The AMA impairment rating is based upon the reduction of lung function coupled with the ability to perform daily living activities. A medical evaluation should be performed which should note specific symptoms, along with the severity, duration and manner of onset of the symptoms. Major symptoms include dyspnea (difficulty breathing), cough, sputum production, hemoptysis (blood in sputum), wheezing, and chest pain/tightness. Dyspnea is non-specific since it can be a symptom from diseases in other systems such as cardiac, hematologic or neurologic. The AMA follows the ATS classification for categorizing the severity level of dyspnea, which is the lowest level of physical activity and exertion which produces breathlessness: mild (the individual walks more slowly for their age level due to breathlessness), moderate (stops for breath when walking at own pace), severe (stops for breath after 100 yards or after a few minutes of walking at own pace) and very severe (the individual is unable to leave their home, breathless while dressing). A thorough medical history is taken in addition to a physical exam which should include imaging (e.g., chest radiographs, CT scans), laboratory studies and pulmonary function tests.

Pulmonary function tests are considered the most useful tool and are the framework for the evaluation of respiratory impairment. The tests listed by the AMA to be performed are:

- forced expiratory maneuvers with spirometry[58] which provide measurements of forced vital capacity (FVC). FVC is the amount of air that can move in and out of the lungs in a single breathing cycle and therefore is a dynamic measurement of lung volume.
- forced expiratory volume in the first second ($FEV_1$). $FEV_1$ assesses air flow dynamics within the bronchi

[57] *Guides to the Evaluation of Permanent Impairment, 5th Edition, AMA Press, 2001.*

[58] Spirometry measures how well the lungs exhale. In a spirometry test, a person breathes into a mouthpiece that is connected to an instrument called a spirometer. The spirometer records the amount and the rate of air that is breathed in and out over a period of time.

- the ratio of FVC and $FEV_1$
- the diffusing capacity for carbon monoxide (Dco) which provides information on gas transfer efficiency across the lungs.

Cardiopulmonary testing can be performed with exercise though the AMA recommends that if done, it is to be carried out judiciously due to potential risk and expense. However it can help differentiate pulmonary impairment from cardiac impairment or from poor physical condition. The exercise capacity is measured by oxygen consumption per unit time ($Vo_2$) or in metabolic equivalents (METS), which is the energy expenditure.

For the AMA impairment rating (class 1-4), the individual must fulfill at least one criterion to be categorized into a specific classification (other than non-impaired). Reference tables are provided in the guide for normal values and lower limits of FVC, $FEV_1$ and Dco. The forced expiratory maneuvers should be performed at least three times and, if possible, with no pulmonary medicines taken twenty-four hours before testing. An adjustment factor is applied for African American $FEV_1$ and FVC values (0.88 of predicted value) and for Dco (0.93 of predicted value) since Caucasians have higher spirometry values. In addition, morbid obesity and anemia need to be taken into account since obesity will reduce FVC values and anemia will reduce Dco. The impairment classification class for respiratory disorders is based upon pulmonary function and exercise test results:

- Class 1, “none”: 0% impairment of the whole person
  - FVC, $FEV_1$, $FEV_1$/FVC and Dco are $\geq$ lower normal limit;
  - $Vo_2$ max is $\geq$ 25ml or 7.1 METS
- Class 2, “mild”: 10-25% impairment of the whole person
  - FVC or $FEV_1$ or Dco is $\geq$ 60% of predicted and below the lower limit of normal
  - $Vo_2$ max is $\geq$ 20ml or 5.7 METS
- Class 3, “moderate”: 26-50% impairment of the whole person
  - FVC is $\geq$ 51% of predicted
  - $FEV_1$ or Dco is $\geq$ 41% of predicted
  - $Vo_2$ max is $\geq$ 15ml or 4.3 METS
- Class 4, “severe”: 51-100% impairment of the whole person
  - FVC is $\leq$ 50% of predicted
  - $FEV_1$ or Dco is $\leq$ 40% of predicted
  - $Vo_2$ max is < 15ml or 4.3 METS

The AMA considers 95% to 100% impairment as a state that is approaching death.

The AMA considers that asthma does not adhere to the strict pulmonary function criteria listed above due to its intermittency. If an individual has frequent, severe attacks even with normal or near normal lung function tests, the AMA would classify them as permanently impaired. For asthma, a severity score is tabulated based on individual scores (0 to 4) for postbronchodilator $FEV_1$, the percentage of $FEV_1$ change, and the minimum medication required. When the $FEV_1$ is greater than the lower limit of normal,

then the degree of airway hyperresponsiveness is based upon $PC_{20}$, the provocative concentration that causes a 20% fall in $FEV_1$. The total asthma score is the summation of the individual scores for $FEV_1$, change in $FEV_1$ and medication use. An asthma score of 0 falls into Impairment Class 1, an asthma score of 1 to 5 is Class 2, an asthma score of 6 to 9 is Class 3, and an asthma score of 10 or above as well as asthma not controlled despite maximal treatment falls into Class 4.

## Skin

Permanent impairment is any dermatologic abnormality or loss that persists after medical treatment/rehabilitation and which is unlikely to change significantly in the next year. In its guidance for determining disability, the Social Security Administration also requires persistence of a skin lesion (despite therapy) in order for a reasonable presumption to be made that a marked impairment will last for a continuous period of at least 12 months. Skin lesions may result in marked, long-lasting impairment if they involve extensive body areas or critical areas such as the hands or feet, and become resistant to treatment. Skin conditions are not covered under the scheduled permanent partial disability provisions of FECA (the Federal Employee's Compensation Act). For classification of permanent impairment, the AMA guidebook indicates that a detailed history should be taken, physical examination performed and diagnostic tests carried out (e.g., patch test, open test, prick test, intracutaneous test, serological test, cultures, biopsies). The frequency, intensity and complexity of the medical condition are to be considered as well as the treatment regimen. Three main criteria are evaluated: (1) signs and symptoms, whether they are intermittent, present or consistently present; (2) the effect on daily living activities; and, (3) the need for treatment and how much is needed. The AMA states that most cutaneous impairment falls within the three classes ranging from 0% to 54%:

- Class 1: 0-9% impairment of the whole person
    - signs/symptoms present or intermittently present
    - no/few limitations on ADL (activities of daily living), or temporary limitation
    - no or intermittent treatment
- Class 2: 10-24% impairment of the whole person
    - signs/symptoms present or intermittently present
    - limited performance of some ADL
    - intermittent to constant treatment
- Class 3: 25-54% impairment of the whole person
    - signs/symptoms present or intermittently present
    - limited performance of many ADL
    - intermittent to constant treatment
- Class 4: 55-84% impairment of the whole person
    - signs/symptoms constantly present
    - limited performance of many ADL, intermittent confinement at home
    - intermittent to constant treatment
- Class 5: 85-95% impairment of the whole person

- signs/symptoms constantly present
- limited performance of most ADL, occasional to constant confinement at home
- intermittent or constant treatment

Contact dermatitis is highlighted in the AMA guidelines. The AMA believes the predominant number of cases evaluated (80%) are due to irritant dermatitis with the remaining from allergic contact dermatitis (ACD). Most irritant cases are from cumulative exposure to marginal irritants which may impair barrier function and therefore allow allergen penetration. If contact continues, then the dermatitis may become chronic and disabiling. In examples provided in the handbooks, one case of severe dermatitis was listed with an impairment classification of 9%, due to the lack of significant impact on daily living activities and intermittent treatment.

## Multiple Organ Systems

When there is permanent impairment to more than one body system, an evaluation of the extent of the whole person impairment related to each system is carried out and the estimated impairment percentages combined (e.g., a dental assistant with severe ACD from latex allergy had a skin impairment rating of 15%; to this the impairment ratings for asthma and rhinitis would be added).

# Appendix C
# Hazard Identification: Criteria for Determining the Severity of Respiratory and Skin Sensitization Responses
### (For possible inclusion in CPSC's revised Chronic Hazard Guidelines)

## Respiratory

Airway hyperresponsiveness (AHR) is a characteristic feature of the lungs of asthmatic individuals. However, it can also be found in individuals with non-allergic conditions of airflow obstruction (e.g., chronic obstructive pulmonary disease [COPD]). Inhaled stimuli, such as environmental allergens, can increase airway inflammation and enhance AHR. These changes in AHR are much smaller in healthy subjects than those seen in asthmatic patients with persistent AHR. However, they are similar to the changes occurring in asthmatic patients that are associated with worsening asthma control, and therefore are useful diagnostic tools for the general population.

Measures of airway responsiveness are based on the increased sensitivity of the airways to an inhaled constrictor (e.g., histamine, methacholine). These non-specific tests are frequently used in making a diagnosis and can be performed quickly, safely, and reproducibly in a clinical or laboratory setting.

In the Institute of Medicine's (IOM) executive summary on indoor allergens, it was recommended that the following testing be considered to diagnose allergy, along with a clinician's review of an individual's medical history:

- skin tests (e.g., skin prick test or patch tests)
- *in vitro* tests (e.g., RAST, ELISA, Ouchterlony)[59]
- pulmonary function tests (e.g., spirometry, peak flow measurements, plethysmography, diffusing-capacity, exercise studies, rhinomanometry)[46].

The National Asthma Education and Prevention Program (NAEPP) was initiated in March 1989 to address the growing problem of asthma in the United States. The NAEPP is administered and coordinated by NIH's National Heart, Lung, and Blood Institute (NHLBI). The NAEPP works with intermediaries including major medical associations, voluntary health organizations, and community programs to educate patients, health professionals, and the public about asthma. The ultimate goal of the NAEPP is to enhance the quality of life for patients with asthma and decrease asthma-related morbidity and mortality. The NAEPP Expert Panel report (#2) provides guidelines for the diagnosis of asthma.[60] These guidelines propose that asthma

[59] RAST (radioallergosorbent test), ELISA (enzyme-linked immunosorbent assay), see Appendix G for definitions

[60] The National Asthma Education and Prevention Program (NAEPP), National Institutes of Health/National Heart, Lung, and Blood Institute. NAEPP Expert Panel, Clinical Practice Guidelines. Expert panel report 2: Guidelines for the Diagnosis and Management of Asthma, volume publication no. 97-4051, Bethesda, MD, 1997; and, NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, Update on Selected Topics 2002.

severity be based on symptomatic and functional assessments, including the frequency and severity of asthma symptoms, the frequency of rescue medication use, and objective measures of lung function. Although several publications indicate that the NAEPP guidelines may not provide clear delineations between all levels of symptoms within the severity classification, [61] these guidelines are in line with the AMA respiratory impairment guidelines and tests recommended by the IOM.

Tests of pulmonary function (particularly $FEV_1$ and PEV measurements)[62], are considered the most useful, and are the framework of the severity determination detailed in the NAEPP guidelines. Medical history, medication use, and symptomatology (type of symptom, severity, duration and manner of onset) are also considered in the NAEPP guidelines. In the "Disease Severity Classification Scheme" recommended in the current NAEPP guidelines, patients are assigned to the most severe grade of asthma in which any feature occurs.

CPSC staff proposes for the determination of the severity of the allergic response that the "moderate persistent" and "severe persistent" classification categories be considered "severe" responses in line with the FHSA "strong sensitizer" supplemental definition. A substance in this "strong sensitizer" category would be considered "toxic" under the FHSA. If it is concluded that a substance is "toxic" under the FHSA, then an assessment of exposure and risk is performed to evaluate whether the chemical/product may be considered a "hazardous substance" under the FHSA.

[61] Fuhlbrigge AL et. al., Am J Respir Crit Care Med 2002, 166:1044-49; Rosenwasser LJ et. al., Pharm Therap 2003 June, 28(6):400-14

[62] FEV (forced expiratory volume) and PEV (Peak Expiratory Volume, also known as peak expiratory flow). Described in Appendices A and G.

| | Symptoms | Nighttime Symptoms | Lung function | Medications[63] | **Considered Toxic Under the FHSA** |
|---|---|---|---|---|---|
| **Mild Intermittent** | Occurring ≤ 2x/ week; asymptomatic and normal PEF between exacerbations; exacerbations brief (few hours for a few days); variable | ≤2x/month | $FEV_1$ or PEF>80% predicted; PEF variability <20% | Long-term: no daily medications needed; systemic corticosteroids may be required for exacerbations. | **No** |
| **Mild Persistent** | Occurring >2x per week but less than 1x/day; exacerbations can affect activity levels | >2x/month | $FEV_1$ or PEF>80% predicted, PEF variability 20%-30% | Long-term: low-dose inhaled corticosteroids; or cromolyn sodium, leukotriene modifiers, nedocromil or sustained release theophylline. | **No** |
| **Moderate Persistent** | Daily; daily use of short-acting $beta_2$ agonists; exacerbations affect activity levels; exacerbations occur ≥1x/week; can last several days | >1x/week | $FEV_1$ or PEF >60% and <80% predicted; PEF variability >30% | Long-term: low-to-medium dose of corticosteroids *and* long-acting inhaled $beta_2$ agonists or with leukotriene modifier or theophylline. | **Yes** |
| **Severe Persistent** | Continual; limited physical activity; frequent exacerbations | Frequent | $FEV_1$ or PEF ≤ 60% predicted; PEF variability >30% | Long-term: high-dose corticosteroids *and* long-acting $beta_2$ agonists *and* (if needed) corticosteroid tablets or syrup. | **Yes** |

(FEV1=forced expiratory volume in one second, PEF=peak expiratory flow)

[63] Short term therapy is the same for each of the four NAEPP classification groups: short-acting beta2 agonist inhaler (two to four puffs as needed); intensity of treatment depends on severity; use of quick-relief more than 2x/week indicates need to step up long-term control therapy.

## Skin

Allergic dermatitis is characterized by erythematous macules (discolored spots) and papules (pimple-like elevated areas on the skin which usually precede vesicle and pustule formation), edema, fluid-filled vesicles or bullae (blister-like), and chronically, by lichenification (thickening) and scaling. Diagnosis is primarily based on skin appearance and history of exposure. There is a lack of consensus as to which visual variables best reflect dermatitis severity and a lack of standardization in disease severity scoring. More than 50 different clinical scoring systems have been identified in the 93 randomized controlled clinical trials published between 1994 and 2001.[64]

The presence or absence of sleep disturbance, the number and location of involved sites and the clinical course are the indicators of severity (i.e., criteria) which provide the best basis for making clinical decisions and severity scoring.[65] Three systems were considered to assess severity: W-AZS, Emerson et al[66] and IGADA (Investigator Global Atopic Dermatitis Assessment)[67]. These systems utilize some or all of the above mentioned criteria. CSPC staff proposes utilizing a simplified version of the W-AZS severity scoring system[68] because it encompasses detailed assessment of both subjective and objective signs and symptoms of dermatitis. It is noteworthy for consideration of both acute and chronic skin manifestations of the disease, for its ease of use, and for its evaluation of pruritus (itching) and loss of sleep. A severity score totaling from 99 points to 152 points would be considered "moderately severe", and a severity score of 153 or more would be considered "severe". Both "moderately severe" and "severe" scores would be considered "toxic" under the FHSA (the maximum severity score is 212).

[64] Charman CR et. al., Arch Dermatol 2005 Sep; 141:1146-51.
[65] Williams HC, NEJM 2005 June; 352(22):2314-24.
[66] Emerson RM et. al., Br J Derm 2000; 142:288-97; who adapted the Rajka & Langeland index, an index which has been widely used as the basis for some of the more common severity scoring systems. This adaptation is simple and has been utilized in clinical trials and is significant because it incorporates chronicity, extent and intensity of disease. The three part score evaluates loss of sleep, clinical course and extent of body surface affected.
[67] Schachner LA et. al., Pediatrics 2005 Sept; 116(3):e334-42; IGADA uses scores based on the Physician Assessment of Individual Signs (PAIS) which evaluates the severity (on a scale from 0 to 3) of erythema, edema, excoriations, oozing/weeping/crusting, scaling and lichenification. The IGADA severity score categories are clear, almost clear, mild, moderate, severe and very severe.
[68] Silny W et. al., Acta Dermatov Croat 2005; 3(4):219-24.

- **Severity Index Score = I + II**[69]
  - **I = A + B**
  - **II = (C + D)/10**

**Section I**

| **A. Pruritus** | **Points** |
|---|---|
| 1. No pruritus | 0 |
| 2. Extent | |
| - Single or multiple | 2 |
| - Extensive | 6 |
| 3. Frequency | |
| - < 30 minutes | 2 |
| - Long-lasting | 4 |
| - Constant | 8 |
| 4. Severity | |
| - No scratching | 2 |
| - Scratching | 4 |
| - Anxiety, irritation | 8 |

| **B. Loss of Sleep** | **Points** |
|---|---|
| 1. No loss of sleep | 0 |
| 2. Problems in falling asleep | 3 |
| 3. Night awakening | 6 |
| 4. Sleeplessness | 12 |

**Section II**

**C: Skin lesions**

| **Body areas**: | | | **D: Severity signs of inflammation** | | | |
|---|---|---|---|---|---|---|
| | | | Erythema & edema score | vesicles score | crust scaling score | lichenification score |
| Head and neck | ( ) x 2 + | Face and neck | ( ) x 3 + | ( ) x 3 + | ( ) x 2 + | ( ) = |
| Trunk | ( ) x 8 | Trunk (anterior) | ( ) x 3 | ( ) x 3 | ( ) x 2 | ( ) = |
| Upper Appendages | ( ) x 4 | Right arm | ( ) x 3 | ( ) x 3 | ( ) x 2 | ( ) = |
| Lower Appendages | ( ) x 8 | Right thigh | ( ) x 3 | ( ) x 3 | ( ) x 2 | ( ) = |

**C**: extent of skin lesions (scored from 0 to 3):
- 0 = absence of lesions
- 1 = 1%-10% of skin surface involved
- 2 = 11%-30% of skin surface involved
- 3 = 31%=100% of skin surface involved

**D**: severity of skin inflammation (sum of four criteria, each scored from 0 to 3):
- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

[69] Based on the W-AZS severity scoring system

# Appendix D
# Background Information for Question #3

Recent Environmental Protection Agency (EPA) Scientific Advisory Panels (SAPs) and scientific workshops have addressed the issue of specific testing for sensitizing chemicals, particularly substances inducing contact sensitization. It has been suggested that no thoroughly validated method exists for the induction and detection of respiratory allergens in animal models. At this time, the FDA and European Medicines Agency (EMEA) ask for induction/challenge studies with plethysmography[70] data but will also accept the murine Local Lymph Node Assay (LLNA) or Guinea Pig Maximization Test (GPMT) results for respiratory hypersensitivity testing. In addition, the EMEA requests a local tolerance test. The EPA does not require a specific respiratory hypersensitivity test at this time but requests GPMT, Buehler Assay (BA) or LLNA data for pesticides.

The GPMT and the BA are the primary assays that historically have been utilized for the determination of sensitizing ability of substances. The GPMT uses the highest concentration of a chemical which will cause mild to moderate irritation. This concentration is injected intradermally (with or without adjuvant) multiple times in the guinea pig shoulder. A patch is attached 7 days later with the same concentration of chemical that was injected. Two weeks later the animals are challenged with a maximal non-irritating dose of the same chemical. The area of erythema and edema is evaluated (either grade 0 to 3, or grade 0 to 4). A chemical is classified as a sensitizer if at least 30% of the animals have a positive response (grade 1 or higher). In the BA, a minimal irritating dose is applied to the shaved flank of a guinea pig and occluded for 6 hours. This application is repeated over a two-week period. Two weeks later, a challenge dose with the highest non-irritating dose is applied to the opposite flank. The area of erythema and edema is evaluated (grade 0 to 4). A chemical is classified as a sensitizer if 15% of the animals demonstrate a positive response (grade 1 or higher).

Extensive debate hovers around the LLNA as a stand-alone assay particularly for the determination of sensitization potency. This assay involves a three-day repeat application of the chemical of interest to the mouse ear dorsum. On the fifth day of the study, tritiated-thymidium is injected and five hours later lymph nodes are collected and the cells counted. An $EC_3$ value is an estimated concentration of chemical necessary to elicit a 3-fold increase in lymph node cell proliferative activity. The assay has been adopted as a test guideline by the Organization for Economic and Cooperative Development (OECD)[63] after it was validated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) as an alternative to guinea pig test methods for hazard identification. It was not considered by ICCVAM for potency determinations but only to determine whether something was or was not a sensitizer. Concerns regarding the LLNA include: (1) that the assay is only appropriate for Type I sensitizers; (2) that insufficient numbers of chemical classes have been

[70] Defined in Appendix G

validated; (3) that the assay is an exaggeration of exposure compared to human exposure (which is intermittent), and; (4) that the assay has been validated for hazard identification but not for potency.

An EPA SAP on dermal sensitization issues in May 2004 concluded that a determination of risk should be of a weight of evidence approach involving history, Quantitative Structure Activity Relationships (QSAR), animal, clinical, toxicological and epidemiology data. Currently, no *in vitro* or *in silico* systems have undergone validation. Additional animal tests that could be considered include the mouse IgE test, cytokine profiling assays and the mouse intranasal test.

The mouse IgE test is a test which has been proposed to allow discrimination between dermal and respiratory sensitizers. The assay involves topical exposure to the test material to shaved flanks of the mice. A week later the animals are challenged on the dorsum of both ears with the test material at half the concentration used previously. Twenty-four hours later changes in ear thickness are measured. About a week later, blood is collected, eosinophils counted and serum IgE levels measured. This test is considered to have an advantage over other tests for the determination of relative potency. However, questions have arisen regarding the assay's robustness and variability as well as its measurement of total IgE and not substance-specific IgE. The assay has not been fully validated.

Cytokine profiling is based upon the premise that T-helper 1 (Th1)[64] cytokines are indicative for skin sensitizers and Th2 cytokines[71] for respiratory sensitizers. Investigators have been developing cytokine profiles, significant elevations in specific cytokine levels, which are consistently associated with either respiratory or skin sensitization. Cytokines currently being evaluated are IL-2, IL-6, IL-12 and IFNγ for Th1 responses, and IL-4, IL-5, IL-10 and IL-13 for Th2 responses. However, this assay assumes all respiratory hypersensitivity reactions are IgE-mediated and display Th2 cytokine responses, which has not been demonstrated for all respiratory allergens (e.g., isocyanates, acid anhydrides). Concerns raised over this technique include the impact that dose, route of exposure and method of quantitation could have on the profile. In addition, it is not considered a good assay for potency determination, and the sensitivity of the assay needs improvement.

The mouse intranasal test (MINT) was initially developed to determine the relative allergenicity of detergent enzymes and to serve as an alternative to the guinea pig intra-tracheal test (GPIT). The GPIT is considered a time consuming and expensive assay, requiring a number of animals and multiple rounds of testing. In the MINT, various doses of the enzymes of interest are administered, via intranasal instillation, three times over a ten day period. Serum samples are collected at the end of the second week of the study and analyzed for specific IgG1 antibody. The MINT has been used by some companies to set occupational exposure guidelines (OEGs) but industry-wide acceptance has not been achieved for this model. The MINT assay does not have the

[71] Defined in Appendices A and G

variability in antibody responses seen with other assays because of the mouse strain typically used (BDF1 mice) in the assay. However, different strains of mice have demonstrated very different potency rankings for similar enzymes. The MINT assay is also plagued by inter-laboratory differences, and with its expansion beyond testing just sensitizing enzymes, it has not been considered valid for low molecular weight chemicals.

# Appendix E

## Federal Hazardous Substances Act

Current Definition of "Strong Sensitizer"

The definition of s*ensitization* which appears in section 2(k) of the FHSA (15 U.S.C. §1262(k); restated in 16 CFR 1500.3(b)(9)) as "strong sensitizer" is:

> *a strong sensitizer is a substance which will cause on normal living tissue through an allergic or photosensitive process a hypersensitivity which becomes evident on reapplication of the same substance and which is designated as such by the Commission. Before designating any substance as a strong sensitizer, the Commission, upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has significant potential for causing hypersensitivity.*

The supplemental definitions:

> *- A sensitizer is a substance that will induce an immunologically-mediated (allergic) response, including allergic photosensitivity. This allergic reaction will become evident upon re-exposure to the same substance. Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization.*
>
> *- In determining that a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors. These factors should include any or all of the following (if available):*
>
> - *Quantitative or qualitative risk assessment*
> - *Frequency of occurrence and range of severity of reactions in healthy or susceptible populations*
> - *The result of experimental assays in animals or humans (considering dose-response factors), with human data taking precedence over animal data*
> - *Other data on potency or bioavailability of sensitizers*
> - *Data on reactions to a cross-reacting substance or to a chemical that metabolizes or degrades to form the same or a cross-reacting substance*
> - *The threshold of human sensitivity*
> - *Epidemiological studies*
> - *Case histories*
> - *Occupational studies*
> - *Other appropriate in vivo and in vitro test studies*

*- The minimal severity of a reaction for the purpose of designating a material as a "strong sensitizer" is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:*

- *physical discomfort*
- *distress*
- *hardship*
- *functional or structural impairment*

*These may, but not necessarily, require medical treatment or produce loss of functional activities.*

*- "Significant potential for causing hypersensitivity" is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance, documented medical evidence of allergic reactions obtained from epidemiological surveys or individual case reports, controlled in vitro or in vivo experimental assays, or susceptibility profiles in normal or allergic subjects.*

*- The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory or gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion or inhalation.*

# Appendix F

## Federal Hazardous Substances Act

CPSC Staff Draft Proposed Supplemental Definition of "Strong Sensitizer"

*Sensitizer.* A sensitizer is a substance that will induce a state of immunologically-mediated hypersensitivity (including allergic photosensitivity) following a variable period of exposure to that substance. Hypersensitivity to a substance will become evident by an allergic reaction elicited upon re-exposure to the same substance.

*Significant potential for causing hypersensitivity.* Before designating any substance as a "strong sensitizer", the Commission shall find that the substance has significant potential for causing hypersensitivity. *Significant potential for causing hypersensitivity* is a relative determination that must be made separately for each substance. It may be based on chemical or functional properties of the substance; documented medical evidence of allergic reactions upon subsequent exposure to the same substance obtained from epidemiological surveys or individual case reports; controlled *in vitro* or *in vivo* experimental studies; and, susceptibility profiles (e.g., genetics, age, gender, atopic status) in non-sensitized or allergic subjects.

In determining whether a substance is a "strong" sensitizer, the Commission shall consider the available data for a number of factors, following a weight-of-evidence approach. The following factors (if available), ranked in descending order of importance, should be considered:

- Validated clinical and diagnostic studies
- Epidemiological studies, with a preference for general population studies over occupational studies
- Well-conducted animal studies
- *In vitro* test studies
- Cross-reactivity data
- Case histories

Before the Commission designates any substance as a "strong" sensitizer, *frequency of occurrence and range of severity of reactions* in healthy or susceptible populations will be considered. The minimal severity of a reaction for the purpose of designating a material as a "strong sensitizer" is a clinically important reaction. For example, strong sensitizers may produce substantial illness, including any or all of the following:

- Substantial physical discomfort and distress
- Substantial hardship
- Functional or structural impairment
- Chronic morbidity

A clinically important reaction would be considered one with loss of function and significant impact on quality of life. Consideration should be given to the location of the hypersensitivity response, such as the face, hands and feet as well as persistence of clinical manifestations.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, the threshold of human sensitivity, other data on potency and sensitizer bioavailability, if data is available. Bioavailability is the dose of the allergen available to interact with a tissue. It is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical. Utilization of QSARs and *in silico* data is considered as an adjunct to human and animal data. Currently these techniques are not validated so their usefulness is limited.

*Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin and other organ systems, such as the respiratory tract, gastrointestinal tract or mucosal system (e.g., ocular, oral), either singly or in combination, following sensitization by contact, ingestion or inhalation.

For a product containing a strong sensitizer to be designated a hazardous substance and to require cautionary labeling under the FHSA[72], the product must be capable of causing substantial personal injury or substantial illness during or as a result of customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children.[73] This requires consideration of the route and the level of exposure that can be expected to be presented by the strong sensitizer as it exists in the particular substance. Therefore, the determination of whether a cautionary label is required must be made on a product-by-product basis and is not solely based upon the presence of a strong sensitizer in a product. If a substance containing a strong sensitizer is determined to be a hazardous substance under the FHSA, cautionary labeling, including the signal words “Caution” or “Warning” and an affirmative statement of the hazard could be required (e.g., “may produce allergic reaction by skin contact or if inhaled”). While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic hazards, the manufacturer is required to label a product appropriately according to the FHSA requirements. However, if a toy or other article intended for use by children is a hazardous substance or bears or contains a hazardous substance in such a manner as to be susceptible to access by a child to whom such toy or other article is entrusted, then the product is by definition a “banned hazardous substance” unless specifically exempted by regulation.[74]

[72]The FHSA, at 15 U.S.C. 1261(p), requires cautionary labeling for any article intended or packaged for household use if it contains a hazardous substance.
[73]15 U.S.C. §1261(f)(1)(A)
[74]15 U.S.C. §1261(q)(1)(A)

# Appendix G
# Glossary of Terms

**Adjuvant** - substances that are added in the presence of an allergen to boost the intensity of the immune response
**Allergen** - any substance that causes an allergic reaction
**Alveolitis** - inflammation of the alveoli, which are the cells in the lung where air exchange occurs
**Anaphylaxis** - a sudden severe and potentially fatal allergic reaction in somebody sensitive to a particular substance, marked by a drop in blood pressure, itching, swelling, and difficulty in breathing
**Asthma** - a disease of the respiratory system, sometimes caused by allergies, with symptoms including coughing, sudden difficulty in breathing, and a tight feeling in the chest
**Atopy** – an inherited tendency, a genetic predisposition, to become sensitized and produce IgE antibodies in response to exposure to allergens
**Buehler Assay** - one of the primary animal assays that historically has been utilized for the determination of sensitizing ability (see Appendix D)
**Bullae** – large blisters or skin vesicles filled with fluid
**Bioavailability** - the dose of the allergen to the tissue with which it interacts. It is a reflection of how well the skin or other organ can absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition
**Conjunctivitis** - inflammation of the conjunctiva, the membrane which lines the inner surface of the eyelid as well as the sclera, the white part of the eye
**Cytokine profiling** - an approach for delineating between respiratory sensitizers and skin sensitizers. It is based upon the premise that elevations in Th1 cytokines are indicative for skin sensitizers and elevations in Th2 cytokines for respiratory sensitizers.
**Dco** – diffusing capacity, Dco is measured when a person breathes carbon monoxide (CO) for a short time, often one breath. The concentration of CO in the exhaled air is then measured. The difference in the amount of CO inhaled and the amount exhaled allows for the estimation of how rapidly gas can travel from the lungs into the blood.
**Dermatitis** – local inflammation of the skin, also known as eczema
**Dyspnea** - difficulty in breathing
**$EC_3$ value** - an estimated concentration of chemical necessary to elicit a 3-fold increase in lymph node cell proliferative activity in the local lymph node assay
**Edema** – swelling
**ELISA** - enzyme-linked immunosorbent assay, a quantitative in vitro test for an antibody or antigen in which the test material is adsorbed on a surface and exposed either to a complex of an enzyme linked to an antibody specific for the antigen or an enzyme linked to an anti-immunoglobulin specific for the antibody followed by reaction of the enzyme with a substrate to yield a colored product corresponding to the concentration of the test material
**Erythema** – redness
**FECA** - Federal Employee's Compensation Act
**$FEV_1$** - forced expiratory volume in the first second, $FEV_1$ assesses air flow dynamics within the bronchi

**FVC** - forced vital capacity, which is the amount of air that can move in and out of the lungs in a single breathing cycle and therefore is a dynamic measurement of lung volume.
**GHS** - a globally harmonized system to classify and label hazardous chemicals, whose development was established in 1992 by a United Nations mandate
**GPMT** - Guinea Pig Maximization Test, one of the primary assays that historically has been utilized for the determination of sensitizing ability (see Appendix D)
**Hemoptysis** – the presence of blood in sputum
**ICCVAM** - Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), a committee which coordinates cross-agency issues relating to development, validation, acceptance, and national/international harmonization of toxicological test methods
**Immunoglobulin** - a high molecular weight protein produced by white blood cells during an immune response, an antibody
**In silico** - a computational approach using sophisticated computer models for the determination of sensitizing potential
**In vitro** - in an artificial environment such as a test tube rather than inside a living organism
**In vivo** - existing or carried out inside a living organism, as in a test or experiment
**Irritant Response** - a non-immune mediated response and one that results from direct injury to the tissue. An irritant is any agent that is capable of producing cell damage in any individual if applied for sufficient time and concentration
**LLNA** - local lymph node assay, is a murine *in situ* test that measures the proliferation of the specific T cells in draining lymph nodes following an allergic response; the assay was validated by ICCVAM as an alternative to guinea pig test methods for hazard identification of contact sensitizers
**Matrix** - the mixture or formulation in which the chemical is present in the consumer product
**MEST** - mouse ear swelling test, GHS indicates that this assay could be utilized as a first stage test in the assessment of skin sensitization potential
**MINT** - mouse intranasal test, initially developed to determine the relative allergenicity of detergent enzymes and to serve as an alternative to the guinea pig intra-tracheal test
**NAEPP** – National Asthma Education and Prevention Program, which was initiated in March 1989 to address the growing problem of asthma in the United States. The NAEPP is administered and coordinated by NIH's National Heart, Lung, and Blood Institute
**OECD** – Organisation of Economic and Co-operative Development, the OECD grew out of the Organisation for European Economic Co-operation (OEEC) which was set up in 1947 with support from the United States and Canada to coordinate the Marshall Plan for the reconstruction of Europe after World War II. The OECD is a forum where the governments of 30 market democracies work together to address the economic, social and governance challenges of globalization as well as to exploit its opportunities. The OECD governments compare policy experiences, seek answers to common problems, identify good practice and coordinate domestic and international policies. Exchanges between OECD governments flow from information and analyzes provided by a secretariat in Paris. The secretariat collects data, monitors trends, and analyses

and forecasts economic developments. It also researches social changes or evolving patterns in trade, environment, agriculture, technology, taxation and more.
**Ouchterlony** - an assay involving agar gel used to examine antigen-antibody reactions. The specific antibodies from a patient's serum and the allergens (antigens) migrate toward each other through the gel which originally contained neither of these reagents. As the reagents come in contact with each other, they combine to form a precipitate that is trapped in the gel matrix and is immobilized.
**Papules** - small pimple-like elevated areas on the skin which usually precede vesicle and pustule formation
**PEV** – Peak Expiratory Volume (also known as peak expiratory flow), measures how fast and hard a person can breathe out (exhale) air, the maximum flow of air with forced expiration. The peak expiratory flow meter is a small, hand-held device with a mouthpiece at one end and a scale with a moveable indicator at the other end. Peak flow measurements will be lower when the airways are constricted.
**Photoallergy** – an allergic response to a photochemically (UV light) activated substance
**Plethysmograph** – measures lung volume, the patient sits in a sealed transparent box while breathing in and out of a mouthpiece. Changes in pressure inside the box permit determination of the lung volume.
**Pruritis** – itching
**Pustule** – small elevation of skin filled with lymph or pus
**QSARs** - Quantitative Structure-Activity Relationships are mathematical models that relate a quantitative measure of chemical structure to biological activity
**RAST** – radioallergosorbent test, an assay for detecting the presence of specific IgE antibodies. An insoluble matrix containing allergens is reacted with a sample of the patient's antibody-containing serum and then reacted again with anti-human antibodies against individual IgE antibodies
**Rhinitis** - inflammation of the nasal mucosa
**Rhinomanometry** - measures air pressure and the rate of airflow in the nasal passages. There are 3 types of rhinomanometry (anterior, postnasal and posterior; anterior rhinomanometry and acoustic rhinometry are probably the most common methods of clinical measurements of nasal airflow).
**Spirometry** - measures lung capacity, how well the lungs exhale
**Th1** - T-helper 1. Th1 cells are a subset of T lymphocytes which produce specific proteins (a.k.a. cytokines). Cytokines produced by this class of T cells include interferon –gamma (IFNγ), interleukin 12 (IL-12), and tumor necrosis factor-alpha (TNFα).
**Th2** - T-helper 2. Th2 cells are a subset of T lymphocytes which produce specific proteins (a.k.a. cytokines). Cytokines produced by this class of T cells include interleukin 4 (IL-4), IL-5, IL-9 and IL-13.
**Urticaria** - a skin rash, usually occurring as an allergic reaction that is marked by intense itching and small pale or red swellings and often lasts for a few days
**Vesicle** – a blisterlike small elevation on the skin containing serous fluid