UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

This document has been electronically approved and signed.

BALLOT VOTE SHEET

Date: February 13, 2013

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Stephanie Tsacoumis, General Counsel
Kenneth R. Hinson, Executive Director

FROM : Patricia M. Pollitzer, Assistant General Counsel
Andrew J. Kameros, Attorney

SUBJECT : Notice of Proposed Rulemaking – Update to Strong Sensitizer Supplemental Definition and Notice of Availability for Staff's Strong Sensitizer Guidance Document

BALLOT VOTE Due: February 20, 2013

Attached are the following draft *Federal Register* notices for Commission consideration: (A) notice of proposed rulemaking to amend 16 C.F.R. part 1500, to reflect changes to the CPSC's supplemental definition of "strong sensitizer"; and (B) notice of availability for staff's strong sensitizer guidance document.

A. Please indicate your vote on the following options on the notice of proposed rulemaking to revise the supplemental definition of "strong sensitizer":

I. Approve publication of the draft notice in the *Federal Register*.

_____ _____
(Signature) (Date)

II. Approve publication of the draft notice in the *Federal Register*, with changes. (Please specify.)

_____

_____

_____ _____
(Signature) (Date)

III. Do not approve publication of the draft notice in the *Federal Register*.

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

_____

_____

_____

_____ _____
(Signature) (Date)

B. Please indicate your vote on the following options on the notice of availability for the staff's strong sensitizer guidance document:

I. Approve publication of the draft notice of availability in the *Federal Register*.

_____ _____
(Signature) (Date)

II. Approve publication of the draft notice of availability in the *Federal Register*, with changes. (Please specify.)

_____

_____

_____

_____ _____
(Signature) (Date)

III. Do not approve publication of the draft notice of availability in the *Federal Register*.

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

_____

_____

_____

_____ _____
(Signature) (Date)

Attachments: Draft *Federal Register* notices: (1) Notice of Proposed Rulemaking-Update of Strong Sensitizer Supplemental Definition; (2) Notice of Availability of Strong Sensitizer Guidance Document

CPSC staff memorandum on Update to the Strong Sensitizer Definition in 16 CFR Part 1500

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

[CPSC Docket No. CPSC-2013-____]

16 CFR Part 1500

Hazardous Substances and Articles; Administration and Enforcement Regulations: Notice of Proposed Rulemaking; Revisions to Supplemental Definition of "Strong Sensitizer"

AGENCY: Consumer Product Safety Commission.

ACTION: Notice of proposed rulemaking.

SUMMARY: The U.S. Consumer Product Safety Commission (CPSC or Commission) proposes to amend 16 CFR part 1500 to update the supplemental definition of "strong sensitizer" under the Federal Hazardous Substances Act (FHSA).

DATES: Written comments must be received by **[insert date that is 75 days after publication in the Federal Register**].

ADDRESSES: You may submit comments identified by Docket No. CPSC-2013-____, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

To ensure timely processing of comments, the Commission is no longer accepting comments submitted by electronic mail (e-mail) except through www.regulations.gov.

Written Submissions

Submit written submissions in the following way:

Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions), preferably in five copies, to: Office of the Secretary, U.S. Consumer Product Safety Commission, Room 820, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7923.

Instructions: All submissions received must include the agency name and docket number for this proposed rulemaking. All comments received may be posted without change, including any personal identifiers, contact information, or other personal information provided, to http://www.regulations.gov. Do not submit confidential business information, trade secret information, or other sensitive or protected information electronically. Such information should be submitted in writing.

Docket: For access to the docket to read background documents or comments received, go to http://www.regulations.gov.

FOR FURTHER INFORMATION CONTACT: Joanna Matheson, Ph.D., Project Manager, Office of Hazard Identification and Reduction, U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850; telephone (301) 987-2564; jmatheson@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

The FHSA, 15 U.S.C. 1261–1278, requires appropriate cautionary labeling on certain hazardous household products to alert consumers to the potential hazards that a product may present. Among the hazards addressed by the FHSA are products that are toxic, corrosive, irritants, flammable, combustible, or strong sensitizers.

Included within the FHSA's definition of "hazardous substance" is "any substance or mixture of substances" that "is a strong sensitizer," 15 U.S.C. 1261(f)(1)(iv). Section 2(k) of the FHSA, 15 U.S.C. 1261(k), defines "strong sensitizer" as:

> A substance which will cause on normal living tissue through an allergic or photodynamic 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 a strong sensitizer, the Commission, upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has a significant potential for causing hypersensitivity.

On August 12, 1961, the Food and Drug Administration (FDA) (which at that time administered the FHSA), issued regulations under the FHSA that supplemented the statutory definition of "strong sensitizer." The regulations also provided a list of substances that the FDA had determined met the statutory definition for "strong sensitizer." The five substances identified were: (1) paraphenylenediamine and products containing it; (2) powdered orris root and products containing it; (3) epoxy resins systems containing in any concentration ethylenediamine, diethylenetriamine, and diglycidyl ethers of molecular weight less than 200; (4) formaldehyde and products containing 1 percent or more of formaldehyde; and (5) oil of bergamot and products containing 2 percent or more of oil of bergamot. No additional substances have been determined to be "strong sensitizers" by the FDA or the Commission since promulgation of this regulation.

In 1973, the responsibility for the administration of the FHSA was transferred to the Commission, and the supplemental definition of "strong sensitizer" was published in title 16 of the Code of Federal Regulations. On May 30, 1984, the Commission revoked the above supplemental definition of "strong sensitizer." 49 FR 22464. The Commission

concluded at that time that the statutory definition of "strong sensitizer" was adequate for any future regulatory determination that a substance is a strong sensitizer.

On August 14, 1986, the Commission issued a rule supplementing the definition of "strong sensitizer" in the FHSA, 51 FR 29094, which currently is in effect. 16 CFR 1500.3(c)(5). As recommended by a Technical Advisory Panel on Allergic Sensitization (TAPAS), the supplemental definition clarifies how the statutory definition should be interpreted and explains the factors the Commission will consider in determining whether a substance is a "strong sensitizer." The supplemental definition states that an "allergic" response is one that is directed by the immune system, such that a sensitization reaction could not be caused by an irritant or other nonallergenic qualities of the substance. The supplemental definition also clarifies that active sensitizers—substances that produce a sensitivity reaction solely as the result of a person's first exposure to the substance as opposed to after reapplication of the same substance—are included within the class of substances that can be determined to be strong sensitizers. The supplemental definition did not address strong sensitizers that cause hypersensitivity by a photodynamic process, principally because Commission staff was unaware of any household product subject to the FHSA that would cause significant exposure of consumers to a photodynamic chemical.

The current supplemental definition makes clear that a sensitivity reaction could occur after the sensitizer is applied to the body's tissues by contact, ingestion, or inhalation; that relevant exposure is not limited to skin contact; and that targets for hypersensitivity reactions include the skin and other organ systems, such as the respiratory or gastrointestinal tracts, either alone or in combination. The supplemental

definition states that the minimal severity of the reaction caused by the substance for purposes of determining whether the substance is a strong sensitizer is a clinically important allergic reaction and provides examples of such clinically important reactions. Whether a substance has a significant potential for causing hypersensitivity is a relative determination that must be made separately for each substance under consideration by the Commission. The supplemental definition sets forth the criteria to be considered in making this determination. Finally, the supplemental definition provides the quantitative and qualitative factors that the Commission should consider in determining that a substance is a "strong" sensitizer, such as the frequency of occurrence and range of severity in normal and susceptible populations and the results of experimental assays in humans and animals.

Recognizing that the science on sensitization has changed since promulgation of the supplemental definition in 1986, the CPSC convened a panel of scientific experts from academia, industry, and the federal government to examine the available scientific and medical information concerning sensitizers, and if appropriate, propose revisions to the supplemental definition of strong sensitizer.

B. Effect of Strong Sensitizer Determination

The Commission is proposing to revise its supplemental definition of strong sensitizer. Additional Commission action would be needed for any substance to be designated a strong sensitizer. In order for the Commission to issue a rule declaring any particular substance (or product containing that substance) to be a strong sensitizer, it must engage in notice and comment rulemaking, separate from this rulemaking, and make the findings specified in 15 U.S.C. 1261(k), *i.e.*, that based upon consideration of

the frequency of occurrence and the severity of the reaction, the substance has a significant potential for causing hypersensitivity. However, a determination that a substance is a strong sensitizer does not automatically trigger a labeling requirement for products containing that substance. Under the FHSA a substance (or product containing that substance) that is a hazardous substance requires appropriate labeling. 15 U.S.C. 1261(p). If manufacturers of products containing a designated strong sensitizer determine that the strong sensitizer in their products may cause substantial injury or illness as a result of reasonably foreseeable handling or use, that product would be a "hazardous substance" as defined under the FHSA, and therefore would warrant appropriate labeling. Alternatively, where there is uncertainty, the Commission has the option under section 3(a)(1) of the FHSA to determine through notice and comment rulemaking that a product containing a strong sensitizer is a "hazardous substance." Hazardous substances intended or packaged in a form suitable for use in the household that do not bear the appropriate cautionary labeling would be considered "misbranded" in violation of the FHSA. 15 U.S.C. 1261(p).

Such cautionary labeling would be insufficient, however, if a toy or other article intended for the use of children is, bears, or contains a hazardous substance (as that term is defined in section 2(f) of the FHSA), and the hazardous substance is accessible to a child to whom the article is entrusted. Under that scenario, the toy or children's article would be considered a "banned hazardous substance" under section 2(q)(1)(A) of the FHSA unless a particular exemption applies. 15 U.S.C. 1261(q)(1)(A).

C. Proposed Amendment

The proposed amendment to 16 CFR part 1500 clarifies or adds language to the supplemental definition of "strong sensitizer" to eliminate redundancy, remove certain subjective factors, incorporate new and anticipated technology, rank the criteria for classification of strong sensitizers in order of importance, define criteria for "severity of reaction," and indicate that a weight-of-evidence approach will be used to determine the strength of the sensitizer.

1. *Definition of sensitizer*. The current definition of *sensitizer* in Section 1500.3(c)(5) is:

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

The proposed amendment reflects the traditional definition for sensitization; sensitization is a multi-stage immune mediated process which occurs over a period of time. Under the proposed amendment, those substances that sensitize through atypical mechanisms, rather than by inducing an obvious "immunologically-mediated response" will be captured by the assessment process. The proposed amendment also eliminates the last sentence of the current definition based on concerns that it may be misinterpreted such that substances that cause an irritant response only[1] (the response that is noted after the first exposure to a substance is more frequently an irritant response and not an allergic response) could be erroneously included in the category of "strong sensitizers." Typically, allergic responses are the result of a two-step process: (1) induction

[1] An "irritant response" is a nonimmune 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.

(sensitization) which requires sufficient or cumulative exposure to induce an immune response with few or no symptoms and (2) elicitation when an individual who has been sensitized demonstrates symptoms upon subsequent exposures. The phrase "variable period of exposure" is included in the proposed amendment to reflect the latency period which is a characteristic in the development of sensitization.

2. *Definition of significant potential for causing hypersentivity*. Currently, 16 CFR 1500.3(c)(5)(iv) provides:

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

The proposed revision to this section reiterates the statutory requirement that before designating any substance a "strong" sensitizer, the Commission must find that the substance has significant potential for causing hypersensitivity. The proposed revision adds qualifiers for susceptibility profiles—genetics, age, gender, and atopic status— to the list of information or data that may be considered in determining whether a substance has a significant potential for causing hypersensitivity; and the proposed revision also replaces the term "normal" with "non-sensitized." These characteristics are well-known modifiers in the development and exacerbation of allergic responses to chemical sensitizers; and replacing the term "normal" with "non-sensitized" reflects more accurately what would be considered the general control population.

The proposed revision of this section also incorporates a discussion of the factors to be considered in determining whether a substance is a "strong" sensitizer. The current

supplemental definition of "strong sensitizer" contains a separate subsection that sets forth factors that should be considered in determining the strength of a sensitizer. (16 CFR 1500.3(c)(5)(ii)). The current section includes several factors that are subjective rather than quantitative (*i.e*., physical discomfort, distress, hardship) and allows for risk assessment considerations in connection with an analysis that should only be a hazard characterization step. The current definition of *strong* is:

> (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 include any and 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, and other appropriate *in vivo* or *in vitro* test studies.

The proposed amendment eliminates the "quantitative or qualitative risk assessment factor" because the Commission believes this terminology is a source of confusion in that it places a risk assessment step within the hazard identification step of the overall process of determining whether a product containing a strong sensitizer requires labeling. The proposed amendment makes clear that a weight-of-the-evidence approach is to be used in determining the strength of a sensitizer because of the imprecise nature of some of the current factors and the potential lack of information or data available to permit useful consideration of certain factors. Rather than allowing an "any or all" approach to what factors would be considered by the Commission in determining whether a sensitizer is strong, the amendment ranks data sources in order of importance, following the FHSA preference for human data over animal data; and the amendment takes into consideration

the value and relevance that certain data would provide in evaluating the potential of a substance to cause hypersensitivity. For example, the proposed amendment expresses a preference for general population epidemiological studies over occupational studies because the degree of sensitization in the workplace is likely to be greater than that of the general population, due to greater exposure (both in time and concentration) to the sensitizing agent.

The proposed amendment provides that for a substance to be considered a "strong" sensitizer the substance must be found to produce a "clinically important reaction," which is defined as a reaction with a significant impact on the quality of life. Examples of such reactions included in the proposed revision to this section are substantial physical discomfort or distress, substantial hardship, functional or structural impairment, or chronic morbidity. The proposed revision to this section also directs the Commission to consider the location of the hypersensitivity response, such as the face, hands, and feet, and the persistence of clinical manifestations in determining whether the substance produces a "clinically important reaction."

The proposed revision to this section adds several factors the Commission can consider in determining a substance's sensitizing potential, for which validated methods currently do not exist but are in development, such as: Quantitative Structure-Activity Relationships (QSARs), and *in silico*[2] data, along with the caveat that using these techniques would be in addition to consideration of human and animal data. We expect that *in vitro* and *in silico* validated methods will be available as part of an integrated

[2] QSARs 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. Both of these approaches are evolving methodologies that have not yet been validated, but are being pursued as testing options that would reduce the numbers of expensive laboratory and animal experiments being carried out.

testing strategy within the next 5 years, and including these components in the amendment ensures that the definition is compatible with current science. The proposed revision also includes a definition of "bioavailability" (*i.e.*, the dose of the substance available to interact with a tissue and that tissue's ability to absorb the substance and the actual penetrating ability of the substance).

3. *Definition of Normal Living Tissue.* Currently, 16 CFR 1500.3(c)(5)(v) defines *normal living tissue* as:

> 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.

The proposed revision adds a specific reference to mucous membranes, such as ocular and oral systems, as types of normal living tissue upon which a substance can cause a hypersensitivity that warrants a determination that a substance is a "strong sensitizer."

4. *Definition of Severity of Reaction.* The current definition for *severity of reaction* at 16 CFR 1500.3(c)(5)(iii)) states that the minimal severity of a reaction for the purpose of designating a material as a "strong sensitizer" is a clinically important reaction, and provides examples of the types of illnesses that could satisfy this criteria, such as physical discomfort, distress, hardship, or functional or structural impairment.

The proposed amendment eliminates this subsection and incorporates the factors to be considered in determining whether a substance is a "strong" sensitizer into the proposed revised section *Significant potential for causing hypersensitivity.*

D. Staff Guidance and Notice of Availability

Commission staff has developed a guidance document that is intended to clarify the "strong sensitizer" definition and assist manufacturers in understanding how CPSC staff would assess whether a substance and/or product containing that substance should be considered a "strong sensitizer." A Notice of Availability is published elsewhere in this issue of the *Federal Register*, which provides a link to the location on the Commission's website where the staff guidance document can be found.

E. Impact on Small Businesses

Under the Regulatory Flexibility Act (RFA), when an agency issues a proposed rule, it generally must prepare an initial regulatory flexibility analysis describing the impact the proposed rule is expected to have on small entities. 5 U.S.C. 603. The RFA does not require a regulatory flexibility analysis if the head of the agency certifies that the rule will not have a significant effect on a substantial number of small entities. *Id.* 605(b).

The Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of revising the supplemental definition of "strong sensitizer." That assessment found that there would be little or no effect on small businesses and other entities because the proposed amendment, which simply modifies the existing supplemental definition of "strong sensitizer," will not result in product modifications to comply; nor will the revised supplemental definition impose any additional testing or recordkeeping burdens. The obligation to label a product as a "strong sensitizer" and any costs associated with that obligation will not arise until the Commission has designated a substance contained in the product as a "strong sensitizer," which would occur only in connection with a separate notice and comment rulemaking proceeding. Thereafter, we

would assess the potential small business impact of designating the particular substance as a strong sensitizer. Moreover, the proposed amendment is not expected to impose any indirect burden on small businesses or other entities because it is not expected to lead to any additional substances being designated as strong sensitizers that would not be so designated in the absence of the amendment. Based upon the foregoing assessment, the Commission finds preliminarily that the proposed rule would not have a significant impact on a substantial number of small entities.

F. Environmental Considerations

Generally, CPSC rules are considered to "have little or no potential for affecting the human environment," and environmental assessments and environmental impact statements are not usually prepared for these rules (see 16 CFR 1021.5(c)(1)). The Commission does not expect the proposed rule to have any adverse impact on the environment under this categorical exclusion.

G. Executive Orders

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations. Section 18 of the FHSA addresses the preemptive effect of certain rules issued under the FHSA. 15 U.S.C. 1261n. Because this rulemaking would revise a regulatory definition rather than issue a labeling or banning requirement, section 18 of the FHSA does not provide for the proposed rule to have preemptive effect.

H. Paperwork Reduction Act

This rule would not impose any information collection requirements.

Accordingly, this rule is not subject to the Paperwork Reduction Act, 44 U.S.C. 3501–3520.

I. Effective Date

The Administrative Procedure Act generally requires that a substantive rule be published not less than 30 days before its effective date, unless the agency finds, for good cause shown, that a lesser time period is required. 5 U.S.C. 553(d)(3). We propose that the rule would take effect 30 days after publication of a final rule in the *Federal Register*.

List of Subjects in 16 CFR Part 1500

Consumer protection, Hazardous substances, Imports, Infants and children, Labeling, Law enforcement, Reporting and recordkeeping requirements, and Toys.

Accordingly, 16 CFR part 1500 is proposed to be amended as follows:

PART 1500—[AMENDED]

1. The authority citation for part 1500 continues to reads as follows:

Authority: 15 U.S.C. 1261–1278

2. Revise paragraph (c)(5) of § 1500.3 to read as follows:

§ 1500.3 Definitions

* * * * *

(c) *Certain statutory definitions interpreted, supplemented, or provided with alternatives.* The following items interpret, supplement, or provide alternatives to definitions set forth in section 2 of the act (and restated in paragraph (b) of this section):

* * *

(5) The definition of *strong sensitizer* in section 2(k) of the Federal Hazardous Substances Act (restated in 16 CFR 1500.3(b)(9)) is supplemented by the following definitions:

(i) *Sensitizer.* A sensitizer is a substance that is capable of inducing 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 reexposure to the same substance.

(ii) *Significant potential for causing hypersensitivity.* Before designating any substance 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: well-conducted clinical and diagnostic studies, epidemiological studies, with a preference for general population studies over occupational studies, well-conducted animal studies, well-conducted *in vitro* test studies, cross-reactivity data, and

case histories. Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration, and use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP), and good epidemiological practice (GEP).

Before the Commission designates any substance a "strong" sensitizer, frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility will be considered. The minimal severity of a reaction for the purpose of designating a material a "strong sensitizer" is a clinically important reaction. 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 and persistence of clinical manifestations. 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.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, specific human sensitization threshold values, and other data on potency and sensitizer bioavailability, if data are available and methods are validated. 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 factors such as size and composition of the chemical.

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

Dated:_____

_____
Todd A. Stevenson, Secretary
U.S. Consumer Product Safety Commission

DRAFT

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

Notice of Availability of Strong Sensitizer Guidance Document

AGENCY: Consumer Product Safety Commission.

ACTION: Notice of availability.

SUMMARY: The U.S. Consumer Product Safety Commission (CPSC or Commission) is announcing the availability of a document prepared by CPSC staff titled, "Strong Sensitizer Guidance." This guidance document is intended to clarify the "strong sensitizer" definition, assist manufacturers in understanding how CPSC staff would assess whether a substance and/or product containing that substance should be considered a "strong sensitizer," and how the Commission would make such a determination.

ADDRESSES: The guidance document is available from the Commission's website at [insert link]. Copies may also be obtained from the Consumer Product Safety Commission, Office of the Secretary, Room 820, 4330 East West Highway, Bethesda, MD 20814; telephone 301-504-7923.

FOR FURTHER INFORMATION CONTACT: Joanna Matheson, Ph.D., Project Manager, Office of Hazard Identification and Reduction, U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850; telephone (301) 987-2564; jmatheson@cpsc.gov.

SUPPLEMENTARY INFORMATION: Elsewhere in today's **FEDERAL REGISTER**, the Commission is publishing a notice of proposed rulemaking for the purpose of revising the supplemental definition of "strong sensitizer" found at 16 CFR 1500.3(c)(5). The Commission is proposing to revise the supplemental definition of

"strong sensitizer" due to advancements in the science of sensitization that have occurred since the current supplemental definition of "strong sensitizer" was promulgated in 1986. Toward this end, the Commission convened a panel of scientific experts from academia, industry, and the federal government who evaluated the current definition in light of scientific advances in the field of sensitization and made recommendations for proposed changes to the current definition, which eliminate redundancy, remove certain subjective factors, incorporate new and future technology for determining the sensitization characteristics of substances, rank the criteria for classification of strong sensitizers in order of importance (*e.g.*, human over animal data), define criteria for "severity of reaction", and adopt a weight-of-the-evidence approach to determine the strength of the sensitizer.

Commission staff has prepared a document titled, "Strong Sensitizer Guidelines," which explains and clarifies each section of the proposed "strong sensitizer" supplemental definition by explaining the current scientific rationale underlying the methodologies and analysis that staff will consider when assessing whether a substance is a strong sensitizer. The CPSC expects that the guidance document will assist manufacturers and other stakeholders in understanding how CPSC staff and the Commission would assess whether a substance or product containing a substance should be considered a "strong sensitizer." The staff guidance document is available on the Commission's website at: [INSERT LINK] and from the Commission's Office of the Secretary at the location listed in the **ADDRESSES** section of this notice.

Dated:_____

_____

Todd A. Stevenson, Secretary

DRAFT

U.S. Consumer Product Safety Commission

Staff Briefing Package

Federal Hazardous Substances Act: Proposed Update to the Strong Sensitizer Supplemental Definition and Staff's Strong Sensitizer Guidance Document

February 13, 2013

Table of Contents

Executive Summary

Executive Summary:

"Strong sensitizer" is one of the seven categories of hazards defined under the Federal Hazardous Substance Act (FHSA). The authority for the FHSA resided with the U.S. Food and Drug Administration (FDA) until it was transferred to the U.S. Consumer Product Safety Commission (CPSC) in 1973. Since its inception in 1972, the 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. In addition, Congress amended the FHSA in 1988, to include the Labeling of Hazardous Art Materials Act (LHAMA) requirements. LHAMA requires art material labels to contain a list of sensitizers present in sufficient amounts to contribute significantly to known skin or respiratory sensitization.

Recognizing that the science on sensitization has changed since the supplemental definitions were published, a panel of scientific experts from academia, industry, and the federal government was convened in 2005, to provide CPSC staff with scientific input. Based on this input, CPSC staff developed and posted a draft technical report on the CPSC website for public comment and solicited federal agency and external scientific peer review. Based upon the public and peer review comments, staff revised the supplemental definition and developed a guidance document.

CPSC staff recommends that the Commission issue a proposed rule revising the supplemental definition of "strong sensitizer" to align with current science and that staff post on the CPSC website a guidance document that describes the major factors that CPSC staff would consider when evaluating products that could contain strong sensitizers.[1] Staff recommends that the rule revising the supplemental definition take effect 30 days after publication of a final rule in the *Federal Register*. Staff believes that 30 days is an appropriate period because the change in the supplemental definition will not have an immediate impact on any products.

Staff recommends revising the supplemental definition to: eliminate redundancy; remove subjective factors; incorporate new and future technology (available within the next 5 years); rank the criteria for classification of strong sensitizers in order of importance (*e.g.*, human over animal data); define criteria for "severity of reaction" (which is undefined in the existing definition and is a critical consideration for declaration of a "strong sensitizer"); and indicate that a weight-of-evidence approach will be used.

Staff believes that the strong sensitizer guidance document provides a stepwise approach in clarifying each section of the strong sensitizer supplemental definition. Each section incorporates the current science rationale behind the potential decision making. The document

[1] CPSC is the only regulatory agency (national and international) that regulates on the basis of a substance being a strong sensitizer (the others only regulate based on whether a substance is a sensitizer). Because of CPSC staff's effort, this option of strong sensitizer was incorporated into the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) chapter on sensitization, which would allow countries that are part of the GHS to use this approach for classifying and labeling chemicals.

should assist manufacturers and other stakeholders in understanding how CPSC staff would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer."

Staff believes that the recommended changes to the strong sensitizer supplemental definition and issuance of the strong sensitizer guidance document would not place any additional requirements on manufacturers. Instead, these activities should clarify for manufacturers the criteria for identifying products that may contain a strong sensitizer. This clarification could reduce unnecessary or expensive testing performed by manufacturers. Furthermore, the recommended changes to the supplemental definition align more closely with internationally harmonized criteria for sensitizing substances.

Briefing Memo

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

This document has been electronically approved and signed.

Memorandum

Date: February 13, 2013

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Stephanie Tsacoumis, General Counsel
Kenneth R. Hinson, Executive Director
Robert J. Howell, Deputy Executive Director for Safety Operations

FROM : J. DeWane Ray, Assistant Executive Director, Office of Hazard Identification and Reduction
Joanna M. Matheson, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT : CPSC Staff's Proposed Update to the Strong Sensitizer Supplemental Definition and Proposed Strong Sensitizer Guidance Document

The attached memo provides the U.S. Consumer Product Safety Commission (CPSC) staff's recommendation that the Commission issue a proposed rule revising the "strong sensitizer" supplemental definition under the Federal Hazardous Substances Act (FHSA) and that staff provide a guidance document describing the major factors that staff considers when evaluating products that could contain strong sensitizers.

I. BACKGROUND

"Strong sensitizer" is one of the seven hazards defined under the FHSA. The authority for the FHSA resided with the U.S. Food and Drug Administration (FDA) until it was transferred to the CPSC in 1973. Since its inception in 1972, the CPSC has not designated any substances to be strong sensitizers.

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. In addition, Congress amended the FHSA in 1988, to include the Labeling of Hazardous Art Materials Act (LHAMA) requirements. LHAMA states that 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 known skin or respiratory sensitization.

Recognizing that the science on sensitization has changed since the supplemental definitions were enacted, a panel of scientific experts from academia, industry, and the federal government was convened by CPSC in 2005, to provide CPSC staff with scientific input. The objective of the panel was to examine the available scientific and medical information concerning sensitizers

and, if appropriate, propose revisions to the supplemental definition of "strong sensitizer," based on the members' knowledge, as scientific experts in this field.

The panel met at the CPSC in early 2006, and in late 2006, CSPC staff's draft technical report was posted on the CPSC website for comment. In 2007, the technical report underwent U.S. federal agency peer review (by staff from the National Institute of Occupational Safety and Health, the National Institutes of Health's National Institute of Environmental Health Sciences and National Institute of Allergy and Infectious Diseases, and the FDA). Peer review comments were addressed by CPSC staff, and in late 2007, the draft technical report underwent external scientific peer review. The external peer reviewers were tasked with evaluating the staff's draft technical report and its appendices and assessing whether the report reflected the current state of the science. In 2008, the draft of staff's technical report was revised and updated, taking into consideration the comments from the external peer review.

II. PROPOSED UPDATED DEFINITION AND STAFF GUIDANCE (TAB A)

This briefing package describes:

(1) staff's recommendation for a proposed revision of the FHSA's supplemental definition of "strong sensitizer" to align with current science, and

(2) staff's guidance document, which describes the major factors that the Commission (or CPSC staff) would consider when evaluating products that could contain strong sensitizers.

III. BENEFITS OF PROPOSED CHANGES

Staff believes that the proposed changes to the definition take an unwieldy definition and update it to align with the statutory definition. The proposed changes to the supplemental definition eliminate redundancy; remove subjective factors; incorporate new and future technology (available within the next 5 years); rank the criteria in order of importance (*e.g.*, human over animal data), which would be used in determining the potential for hypersensitivity; define the criteria for "severity of reaction" (which is undefined in the existing definition and is a critical consideration for declaration of a "strong sensitizer"); and indicate that a weight-of-evidence approach will be used.

Staff believes that its strong sensitizer guidance document provides a stepwise approach in clarifying each section of the strong sensitizer supplemental definition. Each section incorporates the current scientific rationale for the potential decision making. The document should assist manufacturers and other stakeholders in understanding how CPSC staff would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer" (Tab B). Staff would post the guidance document on the Commission's website. Staff recommends that the Commission publish a notice of availability in the *Federal Register* to direct attention to staff's guidance. Staff would be able to revise the document in the future, based on public comments or changes in the relevant science.

IV. OVERALL IMPACT OF DEFINITION AND GUIDANCE

Staff believes that the proposed changes to the strong sensitizer supplemental definition and the strong sensitizer guidance document do not place any additional requirements on manufacturers, but in fact, clarify and limit labeling requirements under the FHSA. Staff also believes that the proposed changes could reduce unnecessary or expensive testing performed by manufacturers.

The guidance document explains how staff uses available scientific information to determine if a product contains a sensitizer that would be considered a strong sensitizer. The proposed definition makes clear that only strong sensitizers that are hazardous substances need to be labeled under the FHSA.

CPSC is the only regulatory agency (national or international) that regulates on the basis of a substance being a strong sensitizer (the others regulate based on whether a substance is a sensitizer). The recommended revisions to the definition of "strong sensitizer" would increase harmonization with the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS). The GHS is a system for standardizing and harmonizing the classification and labeling of chemicals. With the increasingly global use of chemicals and widespread laws and regulations at national, regional, and international levels, the intent of the GHS was to provide an internationally comprehensible system for communicating chemical hazards to all sectors (*e.g.*, consumers, workers, emergency responders, and the public) along the entire life-cycle of the chemical. The GHS is neither a regulation, nor is it a standard. It establishes agreed-upon hazard classification and communication criteria with explanatory information on how to apply the system. The United States (including CPSC staff) participated in the development of the GHS. Because of CPSC staff efforts, the option of strong sensitizer, and the adoption of a weight-of-evidence approach were incorporated into the GHS chapter on sensitization, which would allow countries that are part of the GHS to use these tools to classify and label chemicals.

The Regulatory Flexibility Act (RFA) requires that the Commission consider whether a proposed rule would have a significant economic effect on a substantial number of small entities. Based on available information, CPSC staff believes that there would be no direct burden on small businesses and other entities because, other than the costs to the government associated with developing the updated supplemental definition of "strong sensitizer"— costs that have already been incurred — CPSC staff has not identified any other costs that would result from the draft proposed rule. A manufacturer is not required to label a product as a strong sensitizer or indicate that the product contains a strong sensitizer until the Commission has designated the substance as such; this is done through a separate rulemaking procedure, and either the manufacturer or the Commission has determined that the product meets the FHSA definition of a "hazardous substance." Therefore, amending the supplemental definition of "strong sensitizer" will not impose any new direct obligation on any manufacturer (Tab C). Therefore, the Commission could conclude that the proposed rule recommended by CPSC staff is not expected to have a significant economic effect on a substantial number of small entities.

Under the National Environmental Policy Act (NEPA), the Commission is required to consider the potential environmental impacts that would result from a proposed rule. CPSC staff does not

believe that this proposed rule will have any adverse environmental consequences (Tab C). Therefore, the Commission could conclude that the proposed rule recommended by CPSC staff should not have adverse environmental consequences.

V. STAFF RECOMMENDATIONS

CPSC staff recommends that the Commission issue: (1) a notice of proposed rulemaking (NPR) to revise the supplemental definition of "strong sensitizer" to align with current science, and (2) a notice of availability for the staff guidance document that describes the major factors that CPSC staff would consider when evaluating products that could contain strong sensitizers.

Staff proposes that the rule revising the supplemental definition take effect 30 days after publication of a final rule in the *Federal Register*. Staff believes that 30 days is an appropriate period because the change in the supplemental definition will not have an immediate impact on any products.

Staff recommends posting the Strong Sensitizer Guidance Document on the CPSC website. A draft FR notice stating the availability of the staff guidance document can be found at Tab D.

TAB A: Directorate for Health Sciences Staff Memo

TAB A

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

This document has been electronically approved and signed.

Memorandum

Date: February 13, 2013

TO : Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Toxicology and Risk Assessment

FROM : Joanna M. Matheson, Ph.D., Toxicologist, Division of Toxicology and Risk Assessment

SUBJECT : Health Sciences Assessment: Proposed Update to the "Strong Sensitizer" Supplemental Definition and Proposed Strong Sensitizer Guidance Document

I. Background

A. The FHSA and Reasons for Recommendations Concerning the "Strong Sensitizer" Supplemental Definition

Under the FHSA, the Commission can designate a substance[2] as a strong sensitizer. A substance so designated could be a "hazardous substance" under the FHSA, if the substance or mixture of substances causes substantial personal injury or substantial illness during, or as a proximate result of, any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children. The FHSA requires products that meet the above definition of "hazardous substance" to bear labeling that alerts consumers to the potential hazards that those products present.[3] Thus, whether a product must be labeled depends on its contents and the likelihood that consumers will be exposed to any hazards it presents, such that it causes substantial personal injury or substantial illness.

Revising the supplemental definition of "strong sensitizer" as staff recommends would make the definition consistent with current science and would define more clearly the criteria that should be considered in determining whether a substance and/or product is a strong sensitizer. In addition, staff has developed a Strong Sensitizer Guidance Document (Appendix C) similar to (and as a supplement to) the FHSA Chronic Hazard Guidelines[4] (57 FR 46626, 1992). This

[2] The term "substance" for strong sensitizers can mean the chemical as well as products containing the chemical. For example, "paraphenylenediamine and products containing it" are listed as meeting the definition for strong sensitizer in FHSA section 1500.13, "Listing of 'strong sensitizer' substances."
[3] A toy or other article intended for use by children which is, bears, or contains a hazardous substance (as defined by the FHSA) that a child to whom the article is entrusted may access, is considered a "banned hazardous substance" under section 2(q)(1)(A) of the FHSA, unless an exception applies. 15 U.S.C. §1261(q)(1)(A).
[4] http://www.cpsc.gov/PageFiles/112250/chronic.pdf.

Strong Sensitizer Guidance Document describes some of the major factors that CPSC staff would consider when evaluating products that could contain strong sensitizers (*i.e.*, weight-of-evidence approach using human and animal data). This Guidance Document should assist manufacturers in understanding how CPSC staff would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer." Moreover, the recommended revisions of the definition of "strong sensitizer" would increase harmonization with the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS). The GHS is a system for standardizing and harmonizing the classification and labeling of chemicals. With the increasingly global use of chemicals and widespread laws and regulations at national, regional, and international levels, the intent of the GHS was to provide an internationally comprehensible system for communicating chemical hazards to all sectors (*e.g.*, consumers, workers, emergency responders, and the public) along the entire life-cycle of the chemical. The GHS is neither a regulation, nor is it a standard. It establishes agreed-upon hazard classification and communication criteria with explanatory information on how to apply the system. The United States (including CPSC staff) participated in the development of the GHS. U.S. regulatory agencies are at various stages of determining whether they should implement GHS, and to what extent it should be implemented.

B. Federal Hazardous Substances Act, Strong Sensitizers

The FHSA became public law on July 12, 1960, and it was originally administered by the FDA until that authority was transferred to the CPSC in 1973. Congress enacted the FHSA to provide cautionary labeling for hazardous household substances. "Strong sensitizer" is one of the seven categories of hazards defined under the FHSA. The definition of "*strong sensitizer"* that appears in section 2(k) of the FHSA (15 U.S.C. §1262(k) and restated in 16 C.F.R. §1500.3(b)(9)) is:

> *Strong sensitizer means a substance which will cause on normal living tissue through an allergic or photodynamic 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[5]:

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

Since its inception in 1972, the CPSC has not designated any substances to be strong sensitizers. However, in 1986, the Commission issued a rule clarifying the FHSA's "strong sensitizer"

[5] 16 C.F.R. §1500.13.

definition, with supplemental definitions, as recommended by a Technical Advisory Panel on Allergic Sensitization (TAPAS).[6] The following supplemental definitions were intended to clarify the interpretation of the statutory definition of a "strong sensitizer":

> *(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 reexposure to the same substance. Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization.*
>
> *(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*
>
> *(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.*
>
> *(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*

[6] 16 C.F.R. §1500.3(c)(5.)

surveys or individual case reports, controlled in vitro or in vivo experimental assays, or susceptibility profiles in normal or allergic subjects.

(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.

Congress amended the FHSA in 1988, to include the Labeling of Hazardous Art Materials Act (LHAMA) requirements. LHAMA did not alter the FHSA definition of strong sensitizer, but it is relevant here. LHAMA requires a review 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.*[7] To protect users from known sensitizers found within art materials, each label shall contain a list of sensitizers present in sufficient amounts to contribute significantly to known skin or respiratory sensitization.[8]

C. Technical Review of Strong Sensitizer Supplemental Definition

A panel of scientific experts from academia, industry, and the federal government was convened in 2005, to review the existing supplemental definition of strong sensitizer and provide CPSC staff with scientific input. The objective of the panel was to examine the available scientific and medical information concerning sensitizers and, if appropriate, propose revisions to the existing FHSA supplemental definition for "sensitization," based on the members' knowledge as scientific experts in this field. The panel met at the CPSC in early 2006, and in late 2006, CSPC staff's draft technical report was posted on the CPSC website for comment. In 2007, the technical report underwent U.S. federal agency peer review (National Institute of Occupational Safety and Health, the National Institutes of Health's National Institute of Environmental Health Sciences and National Institute of Allergy and Infectious Diseases, and the Food and Drug Administration). Peer review comments from the federal agency scientists were addressed, and in late 2007, the draft technical report underwent external scientific peer review. The external peer reviewers were tasked with evaluating the draft staff technical report and its appendices and assessing whether the report reflects the current state of science. In addition, the reviewers were asked to address questions regarding possible linkages of severity of reaction/response to a sensitizer with a substance's sensitizing strength, as well as questions about severity criteria for upper airway and skin hyperreactivity responses.

In 2008, the draft staff technical report was updated, taking into consideration the comments from the external scientific peer review (Tab E). A summary report of the external peer review, along with CPSC's Health Sciences (HS) staff response, was prepared and circulated among

[7] 16 C.F.R. §1500.14(b)(8)(i)(B)(9).
[8] 16 C.F.R. §1500.14(b)(8)(i)(E)(5).

CPSC staff. HS staff recommended updating the supplemental definition, developing a guidance document, and creating a chemical sensitizer database. Based upon these CPSC staff discussions, the supplemental definition was refined further to be the proposed definition outlined later in this memo (also found in Appendix A of this memo).

D. International Activities on Sensitizers

At the same time HS staff was evaluating the FHSA "strong sensitizer" supplemental definition, activities were occurring in Europe on related chemical labeling and classification issues. The GHS is an internationally harmonized approach to classification and labeling for all chemicals and mixtures of chemicals. The CPSC is a member of the U.S. federal interagency work group participating in the development and possible implementation of the GHS. Respiratory and skin sensitizer classification is addressed in GHS Chapter 3.4. HS staff was part of an Organisation for Economic Co-operation and Development (OECD)[9] expert group on sensitization, formed to develop the first version of the GHS sensitizer chapter, as well as a revised GHS approach on sensitizers relating to sensitizing strength.

Because of CPSC staff's participation in this expert group, components of the FHSA "strong sensitizer" definition are now part of the GHS sensitization criteria, including consideration of the frequency of occurrence and the extent of exposure to a sensitizing substance. The OECD sensitization expert group met for the final time in March 2008, at the CPSC, to continue work on the United Nations' (UN) request for a proposal to revise the GHS chapter with respect to classifying strong versus weak skin sensitizers. One of the issues that came from discussions with the OECD expert group was that of sensitizer potency and tests that can be used to determine potency of chemicals that might be sensitizers. European scientists favored the sole use of the murine Local Lymph Node Assay (LLNA) for the determination of sensitizer potency. Because of concerns about the scientific validity of this approach, CPSC staff nominated the LLNA test method for determination of sensitization potency, to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for its review.[10] ICCVAM was requested, in particular, to review the validation status of the use of the LLNA as a standalone

[9]The OECD, officially established in 1961, is an offshoot from the Organisation for European Economic Cooperation established in 1947 for implementation of the Marshall Plan. The OECD is a forum of member countries committed to democracy and the market economy, providing a setting to compare policy experiences, seek answers to common problems, identify good practices, and coordinate domestic and international policies. Its mandate covers economic, environmental, and social issues. As part of the OECD Environment Directorate, the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, manages the Test Guidelines Programme. Because of this expertise, the OECD was the focal point for the development of the GHS classification of health and environmental hazards. The work was coordinated and managed under the auspices of the Interorganization Programme for the Sound Management of Chemicals Coordinating Group for the Harmonization of Chemical Classification Systems.

[10] ICCVAM, a committee created by the National Institute of Environmental Health Sciences in 1993, 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 duties of ICCVAM are to review, optimize, and validate new, revised, or alternative test methods that encourage the reduction, refinement, or replacement of the use of animals in testing.

assay for the determination of potency. The ICCVAM Peer Review Panel (3/3−3/7/08)[11] recommended that the LLNA should be used as part of a weight-of-evidence approach for potency determinations, rather than as a standalone assay.[12] As a result, CPSC staff was able to persuade their European counterparts on the OECD expert panel to agree that the revisions to the GHS sensitization chapter embrace the use of the LLNA as part of a weight-of-evidence approach, not as a stand-alone test, which is in alignment with the proposed revised FHSA strong sensitizer supplemental definition.

The revised GHS chapter was forwarded to the OECD Task Force on Harmonisation of Classification and Labelling of Chemicals, approved by the OECD Task Force, submitted and accepted by the UN Sub-Committee of Experts on the GHS in December 2008, and published in the 3rd revised edition of the GHS in July 2009 (final criteria are found in Appendix B of this memo). HS staff believes that this proposed GHS approach for classifying and labeling chemicals that are sensitizers will generally be compatible with the revisions staff recommends to the FHSA strong sensitizer supplemental definition. Recently, the U.S. Department of Labor's Occupational Health and Safety Administration (OSHA) finalized its implementation of the GHS. It revised its Hazard Communication Standard, aligning it with the GHS. OSHA's final rule became effective in May 2012, and its Hazard Communication Standard is expected to be fully implemented in 2016. OSHA is adopting the subcategories as proposed in the GHS sensitizer chapter, edition 3, for labeling of chemical sensitizers.

In November 2011, ASTM International developed and adopted a voluntary safety standard on children's metal jewelry (F2923-11). This standard addresses nickel, cadmium, hazardous magnets, and certain chemicals in surface coatings in children's metal jewelry, and it incorporates limits on nickel migration, consistent with international jewelry standards.[13]

II. Recommended Changes to the Supplemental Strong Sensitizer Definition

Currently, determining whether a substance is a strong sensitizer under the FHSA supplemental definition is complex. Staff believes that its draft proposed revisions to the supplemental definition of "strong sensitizer" will help clarify the definition. For any new candidates, the Commission would have to designate a substance as a "strong sensitizer," and that substance

[11] Thus, two expert groups (with some common participants), the OECD expert group and the ICCVAM Panel, were concurrently addressing issues on the LLNA, including the issue of sensitizer potency.

[12] On December 28, 2011, the Commission voted unanimously to approve the recommendation that the LLNA should not be considered a standalone assay for skin sensitization potency classification.

[13] Allergy to nickel is a common cause of contact dermatitis, with roughly 10 percent of the population in Western Europe and North America being sensitive to nickel. Initial sensitization frequently occurs from jewelry, such as ear studs and other body piercings; and nickel allergy is more prevalent among women than men. Once sensitized, an individual can develop contact dermatitis from shorter-term contact with nickel-containing products. This led to moves by two European countries to prevent the initial sensitization of jewelry wearers, by limiting the use of nickel in piercing studs and other products that are in prolonged contact with the skin; and then to the European Union Nickel Directive in 1994. With the publication of this ASTM standard, firms can test and confirm conformance to the standard.

would have to meet the FHSA definition of "hazardous substance" before labeling would be required. The revised supplemental definition that staff recommends is as follows:

(i) *Sensitizer.* A sensitizer is a substance that is capable of inducing 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 reexposure to the same substance.

(ii) *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 hypersensitivity 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.[14] The following factors (if available), ranked in descending order of importance, should be considered:

(A) well-conducted clinical and diagnostic studies;
(B) epidemiological studies, with a preference for general population studies over occupational studies;
(C) well-conducted animal studies;
(D) well-conducted *in vitro* test studies;
(E) cross-reactivity data;
(F) case histories.

Criteria for a "well-conducted" study would include: validated outcomes, relevant dosing and route of administration, and use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP), and good epidemiological practice (GEP).

Before the Commission designates any substance as a "strong" sensitizer, *frequency of occurrence and range of severity of reactions* in exposed

[14] Weight-of-evidence is an evidence-based approach that involves an assessment of the relative values/weights of all available information. It is a consideration of the strengths and weaknesses of the available data, taking into account the quality of the data and consistency of the study results for each endpoint, in reaching and supporting a conclusion concerning the sensitizing potential of a substance.

subpopulations having average or high susceptibility 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. A clinically important reaction would be considered one with a 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. For example, strong sensitizers may produce substantial illness, including any or all of the following:

(A) substantial physical discomfort and distress;
(B) substantial hardship;
(C) functional or structural impairment;
(D) chronic morbidity.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs),[15] *in silico* data, specific human sensitization threshold values, other data on potency and sensitizer bioavailability, if data is available and the methods validated. 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.

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

Outline and Discussion of Proposed Revisions

Staff recommends modifying each section of the strong sensitizer supplemental definition. The supplemental strong sensitizer definition was reorganized to reflect a more logical presentation. CPSC staff determined that the cornerstone of the strong sensitizer definition is the determination of the s*ignificant potential for causing hypersensitivity*. The existing "*strong*" and "*severity of reaction*" sections of the supplemental definition each provide criteria that define the s*ignificant potential for causing hypersensitivity*. Therefore, staff determined that a more logical presentation would be to merge these sections under s*ignificant potential for causing hypersensitivity*, thereby removing redundancy (*i.e., severity of reaction* appears in more than one section of the current supplemental definition) and providing clarity to the proposed supplemental definition.

The series of tables below provide a side-by-side view of the existing and corresponding proposed supplemental definition, followed by a brief summary and discussion of the suggested

[15] QSARs are mathematical models that relate a quantitative measure of chemical structure to biological activity.

changes. A detailed discussion of each modification appears in the 2008 staff technical document (Tab E).

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

- *Sensitizer:* In this section, the language will be simplified and the sentence: "*Occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization,"* will be deleted.

  The draft proposed language reflects the classic definition of "sensitization"; sensitization is a multistage immune-mediated process that occurs over a period of time. Even though some sensitizers may not demonstrate an obvious "immunologically mediated" response, for substances that sensitize through atypical mechanisms, the weight-of-evidence approach suggested by staff should ensure that these substances will be captured in the assessment process. Staff believes that the deleted sentence can be misinterpreted, such that substances that cause irritation could be included in the category of "strong sensitizers." Irritant substances are not the same as sensitizers.

Existing supplemental definition	Proposed revised supplemental definition
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, and • other appropriate *in vivo* and *in vitro* test studies.	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: • well-conducted clinical and diagnostic studies; • epidemiological studies, with a preference for general population studies over occupational studies; • well-conducted animal studies; • well-conducted *in vitro* test studies; • cross-reactivity data; and • case histories.

- *Strong*: In this section:
  - The language will be simplified.
  - Terms will be deleted because they are redundant (*e.g.*, *in vivo*) or because they do not contribute to the definition (*e.g.*, quantitative and qualitative risk assessment).
  - A weight-of-evidence approach will be added for the determination of the strength of a sensitizer.
  - The remaining qualifying types of data will be ranked in order of importance, based on preference for human data over animal data.

  While this section of the existing supplemental definition expanded and provided factors that could be considered in determining the strength of a sensitizer, the section included many subjective factors that were not quantitative. This section also introduced risk assessment considerations into what should be solely a hazard-characterization step. Because of the indeterminate nature of these factors and the potential lack of information/data to support the factors, staff recommends that a weight-of-evidence approach be used to determine the strength of a sensitizer. Instead of an "any or all" approach to what criteria would be considered by CPSC staff, the data sources were

ranked in order of importance, following the FHSA preference for human data over animal data and taking into consideration the value and relevance that the particular data would provide in making a determination of sensitizing strength, and thus, the potential to cause hypersensitivity. Furthermore, factors for consideration that were listed separately, and are related, have been combined (*e.g.*, occupational studies, by definition, are a subset of epidemiological studies; animal studies are *in vivo* studies).

Currently, no *in vitro* or *in silico*[16] systems have undergone validation for determining sensitizing potential. Both approaches are evolving methodologies, and both are being pursued actively. It is expected that *in vitro* and *in silico* validated methods will be available within the next 5 years as part of an integrated testing strategy, at least for skin sensitizers. Inclusion of these components in the revised supplemental definition ensures that the definition is compatible with current science.

The CPSC technical panel requested that more specific, and if available, more objective criteria be indicated for evaluating the severity of a reaction in the respiratory system and skin. Staff has developed criteria for determining respiratory and skin allergic response severity (using the National Asthma Education and Prevention Program, NAEPP, guidelines and the W-AZS skin severity scoring system), which are discussed in the strong sensitizer guidance document located in Appendix C.

Existing supplemental definition	Proposed revised supplemental definition
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, and • functional or structural impairment. These may, but not necessarily, require medical treatment or produce loss of functional activities.	Before the Commission designates any substance as a "strong" sensitizer, *frequency of occurrence and range of severity of reactions* in exposed subpopulations having average or high susceptibility 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, and - chronic morbidity. A clinically important reaction would be considered one with a 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.

[16] *In silico* data represent a computational approach, using sophisticated computer models to determine sensitizing potential, rather than use of animals or *in vitro* tests.

- *Severity of reaction*: This section, redundant with "severity of reaction" in the existing section (*ii) strong,* will be moved and included in the proposed revised section: "*Significant potential for causing hypersensitivity,"* which contains the criteria assessed for "strong."

Existing supplemental definition	Proposed revised supplemental definition
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.	*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 hypersensitivity 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.

- *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. These characteristics are well-known modifiers in the development and exacerbation of allergic responses to chemical sensitizers. The term "normal" will be replaced with "non-sensitized" to reflect more accurately what would be considered the general control population. This paragraph will be moved to introduce the second section of the proposed supplemental definition, such that the criteria that are considered in determining the potential for causing hypersensitivity follow and are ranked in order of importance.

Existing supplemental definition	Proposed revised supplemental definition
There is no existing section. Some of the factors were listed in the section "*Strong*".	Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, specific human sensitization threshold values, other data on potency and sensitizer bioavailability, if data are available and the methods validated. 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 factors such as size and composition of the chemical.

- This is a new section that appears at the end of the reorganized section, "*significant potential for causing hypersensitivity.*" This section contains other factors for consideration of sensitizing potential for which validated methods currently do not exist (*e.g.*, *QSARs, in silico* data). Definitions are also provided for some of the qualifiers (*e.g.*, bioavailability) that appear in the "strong" section of the existing supplemental definition.

Existing supplemental definition	Proposed revised supplemental definition
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.	*Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin, mucous membranes (*e.g.*, ocular, oral), and other organ systems, such as the respiratory tract and gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion, or inhalation.

- *Normal living tissue*: In this section, consideration of mucosal membranes, specifically highlighting ocular and oral systems, is added.

III. Strong Sensitizer Guidance Document

HS staff has developed a Strong Sensitizer Guidance Document (Appendix C) similar to, and as a supplement to, the Chronic Hazard Guidelines. This strong sensitizer guidance document describes and discusses some of the major factors that CPSC staff considers when evaluating products that could contain strong sensitizers (*i.e.*, weight-of-evidence approach using human and animal data). The guidance document also contains objective criteria for evaluating the severity of a reaction in the respiratory system and skin. The discussion of the severity criteria indicates the clinical threshold response that staff generally would consider "severe" in determining whether a substance is a strong sensitizer.

This guidance document would clarify the "strong sensitizer" definition, and assist manufacturers in understanding how CPSC staff would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer." Staff recommends posting the Strong Sensitizer Guidance Document on the CPSC's website. A draft FR notice stating the availability of the Sensitizer Staff Guidance Document can be found at Tab D.

IV. Conclusion

CPSC staff recommends that the Commission issue: (1) a notice of proposed rulemaking (NPR) to revise the supplemental definition of "strong sensitizer" to align with current science, and (2) a notice of availability for the staff guidance document that describes the major factors CPSC staff would consider when evaluating products that could contain strong sensitizers.

The recommended changes to the supplemental definition eliminate redundancy, remove subjective factors, incorporate new and future technology, rank criteria for classification of

strong sensitizers in order of importance, define criteria for "severity of reaction," and indicate that a weight-of-evidence approach will be used.

The strong sensitizer guidance document takes a stepwise approach in clarifying each section of the strong sensitizer supplemental definition. Accordingly, the document should assist manufacturers and other stakeholders in understanding the major factors that CPSC staff would consider when evaluating products that could contain strong sensitizers.

Staff believes that the recommended changes to the strong sensitizer supplemental definition and the strong sensitizer guidance document would not place any additional requirements on manufacturers. These clarifications could reduce unnecessary or expensive testing performed by manufacturers. Furthermore, the draft proposed supplemental definition aligns more closely with internationally harmonized criteria for sensitizing substances.

Appendix A
CPSC Staff's Recommended Changes to the Supplemental Strong Sensitizer Definition

The definition of "strong sensitizer" in section 2(k) of the Federal Hazardous Substances Act (restated in 16 C.F.R. §1500.3(b)(9) is supplemented by the following definitions:

(i) *Sensitizer.* A sensitizer is a substance that is capable of inducing 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 reexposure to the same substance.

(ii) *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 hypersensitivity 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:

(A) well-conducted clinical and diagnostic studies;
(B) epidemiological studies, with a preference for general population studies over occupational studies;
(C) well-conducted animal studies;
(D) well-conducted *in vitro* test studies;
(E) cross-reactivity data;
(F) case histories.

Criteria for a "well-conducted" study would include: validated outcomes, relevant dosing, route of administration, and use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP) and good epidemiological practice (GEP).

Before the Commission designates any substance as a "strong" sensitizer, frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility 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. A clinically important reaction would be considered one with a 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. For example, strong sensitizers may produce substantial illness, including any or all of the following:

(A) substantial physical discomfort and distress;
(B) substantial hardship;
(C) functional or structural impairment;
(D) chronic morbidity.

Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, specific human sensitization threshold values, other data on potency and sensitizer bioavailability, if data are available and the methods validated. 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 factors such as size and composition of the chemical.

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

Appendix B

GHS Sensitization Cut-Off Criteria[17] and Sensitization Test Methods

GHS

The GHS describes a scheme for classifying and labeling of chemicals (including mixtures). The GHS is neither a regulation, nor a standard. The aims of the GHS are to address classification of chemicals by type of hazard and propose internationally harmonized hazard communication elements (including labels and safety data sheets), such that the information on physical hazards and toxicity from chemicals is available to protect human health and the environment during the handling, transport, and use of these chemicals. The GHS provides criteria for classification, with explanatory information on how to apply the system. While national governments, regional institutions, and international organizations are the primary audiences for the GHS, the guidance also applies for those in industry who ultimately will be implementing the requirements that have been adopted.

The GHS includes criteria for physical, health, and environmental hazards. The first edition of the GHS, intended to serve as the initial basis for the global implementation of the system, was published in 2003. The ability of a chemical to sensitize an individual is one consideration for classification.

The final criteria adopted by the GHS to distinguish strong skin sensitizers from other sensitizers, are based on appropriate human and/or experimental animal studies (*e.g.*, guinea pig and Local Lymph Node Assay, LLNA, data). Below are excerpts from the third edition, published in 2009, which contain the updates to the sensitization chapter as previously described.

- The hazard categories for both respiratory and skin sensitizers consist of a "Category 1 where subcategorization is not required by a competent authority[18] or where data are not sufficient for subcategorization. Where data are sufficient and where required by a competent authority, a refined evaluation . . . allows the allocation of respiratory (or skin) sensitizers into subcategory 1A, strong sensitizers, or subcategory 1B for other sensitizers." The GHS building block approach allows a competent authority to select the appropriate elements for classification and communication according to their regulatory scheme (*i.e.*, selection of solely subcategory 1A or selection of both subcategories).

[17] The GHS, 3rd edition, is available at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev03/English/03e_part3.pdf.
[18] Examples of competent authorities would be CPSC, EPA, OSHA, and Health Canada.

Hazard category and subcategories for respiratory sensitizers

CATEGORY 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or (b) if there are positive results from an appropriate animal test.
Subcategory 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered.
Subcategory 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered.

Hazard category and subcategories for skin sensitizers

CATEGORY 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer (a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Subcategory 1A:	Substances showing a high frequency of occurrence in humans and/or high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Subcategory 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

In addition, "when considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases:

(a) the size of the population exposed;
(b) the extent of exposure."

- Due to the wealth of data on the strength of skin sensitizing chemicals, specific cutoff criteria are provided in the GHS proposal for skin subcategories 1A and 1B. Specific cutoff criteria are provided for human data and animal test results. The human evidence for a Subcategory 1A, **stronger** sensitizer, can include positive results for the induction threshold at ≤ 500 µg/cm² in human diagnostic patch test data (specifically, the Human Maximization Test [HMT] and the Human Repeat Insult Patch Test [HRIPT]). Animal test results for Subcategory 1A can include data from the murine Local Lymph Node Assay (LLNA) and guinea pig tests (the Guinea Pig Maximization Test and the Buehler Assay). The cutoff values for the animal test results for Subcategory 1A, stronger skin sensitizers, in GHS Table 3.4.3 are below.

Table 3.4.3: Animal test results for Subcategory 1A

Assay	Criteria
Local Lymph Node Assay	EC3 value ≤ 2%[19]
Guinea Pig Maximization Test	≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose
Buehler Assay	≥ 15% responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose

- For classification of mixtures, "when reliable and good quality evidence from human or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by a weight-of-evidence evaluation of these data." Bridging principles[20] are followed "where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture." The cut-off value/concentration limit of ingredients of a mixture classified as a strong sensitizer (Subcategory 1A, skin and respiratory) that would trigger classification of the mixture is ≥ 0.1%. A note is provided stating that "some competent authorities may require a Safety Data Sheet (SDS) and/or supplemental labeling only . . .."

  However, section 1500.5 of the Commission's regulation issued under the FHSA, "Hazardous Mixtures," states: "the mixture itself should be tested." This section indicates that the determination of whether a mixture is a "hazardous substance" should be based on the physical, chemical, and pharmacological characteristics of the mixture. Due to synergistic or antagonistic reactions, a mixture of substances may be more or less hazardous than its components. It may not be possible to reach a fully satisfactory decision concerning the sensitizing properties of a substance from what is known about its components or ingredients.

[19]The EC3 value is the concentration of a test substance that results in a threefold increase in lymphocyte proliferation in the draining lymph node.

[20]Bridging principles are criteria for classifying untested mixtures. When a mixture has not been tested, but there is sufficient data on the components and/or similar tested mixtures, these data can be used in accordance with the following bridging principles: Dilution; Batching; Concentration of highly toxic mixtures; Interpolation within one toxic category/subcategory; Substantially similar mixtures; and Aerosols. Each of these bridging principles is defined within the GHS chapter. For example, the "Dilution" bridging principle is defined as follows: "if a mixture is diluted with a diluent which is not a sensitizer and which is not expected to affect the sensitization of other ingredients, then the new mixture may be classified as equivalent to the original mixture." When the bridging principles do not apply or cannot be used, the health and environmental hazards of mixtures are estimated based on component information.

Past and Current Sensitization Testing

Historically, data on the sensitization potential of chemicals came from studies using human volunteers. Two tests for predicting whether a person will become sensitized to a substance are the HMT and the HRIPT.[21] The HMT is no longer in use, due to ethical concerns about its potential to create adverse health consequences for the person being tested. Contract laboratories have performed the vast majority of human sensitization tests, particularly the HRIPT. There are a limited number of scientific publications with human sensitization data, of which much is derived from older studies (many from the period of the 1960s). The development of animal sensitization tests has been based on a comparison of the human tests performed with the same chemicals.

Prior to development of the LLNA, the Guinea Pig Maximization Test (GPMT) and the Buehler Assay (BA) had been the primary animal assays used to determine the sensitizing ability of a chemical. The GPMT is a highly sensitive method; however, some of the sensitivity arises due to the coadministration of a painful immune stimulant. This method involves injecting under the skin of the animal the possible sensitizer being tested, as well as applying it to the surface of the skin. The BA uses repeat closed topical applications (filter papers containing the test sensitizer of interest are covered with a patch and taped to the skin in order to enhance absorption of the substance). The GPMT is regarded as a more sensitive assay that, for certain substances, also may overestimate the sensitization hazard for the compound tested. The BA is less sensitive and may underestimate the sensitization potential of a compound.

In 1997, the LLNA was proposed as a standalone alternative method to the GPMT and the BA for sensitization hazard identification.[22] In 1999, ICCVAM recommended the LLNA as an alternative test method for assessing the skin sensitization potential of most types of substances. This was based on data collection by ICCVAM to validate the test method. The consensus of the ICCVAM scientific 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 predicting accurately some weak sensitizers and some strong irritants.[23] The LLNA provides several advantages compared to the guinea pig assays, including elimination of potential pain and distress, use of fewer animals, shorter test duration, a more objective end point, less test substance required, and the availability of dose-response information. U.S.

[21] These tests vary with regard to the number of induction patch tests, the placing of the patches, and the use of a maximization step (an amplifying step during the challenge phase, this step involves co-treatment of the test sensitizer of interest with an irritant in order to enhance a potential response).

[22] The LLNA provides a yes/no answer about whether a substance is a sensitizer.

[23] It is important to distinguish a "sensitizer" response from an "irritant" response. Due to the nature of the immune system, in order for an individual to become sensitized to a particular substance, there is a lag sensitization phase (induction), followed by a secondary immune response (elicitation phase). The amount of time and the amount of exposure (the dose), the variable period of exposure, required for sensitization will depend upon the individual. 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. Irritant responses occur without sensitization. Irritant symptoms can occur within minutes of 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. Allergic responses (*e.g.*, allergic contact dermatitis) can be localized but also may have widespread skin involvement, particularly in patients with strong sensitization.

regulatory agencies (including the CPSC) accepted the LLNA as a valid alternative test method for allergic contact dermatitis testing. The LLNA also was adopted as a test guideline (test guideline [TG] 429) in 2002, by the Organization for Economic and Cooperative Development (OECD) after the ICCVAM validation of the assay.

On March 9, 2010, the Commission voted unanimously to approve ICCVAM recommendations, including: (1) updates to the test method protocol; (2) establishment of performance standards; and (3) a modified form of the assay, the reduced Local Lymph Node Assay (rLLNA). The revised LLNA test method protocol and the LLNA performance standards encourage the reduction, refinement, or replacement of animals in testing. On January 26, 2011, the Commission voted to approve the recommendations of ICCVAM regarding an expanded applicability domain and two nonradioactive versions of the LLNA: (1) the Bromodeoxyuridine Enzyme-linked Immunosorbent Assay (BrdU-ELISA); (2) the Daicel Chemical Industries version (LLNA:DA), which have been adopted by the OECD, as Test Guideline 442B and Test Guideline 442A, respectively. These alternative, nonradioactive LLNA test method protocols encourage the reduction, refinement, or replacement of animals in testing and the data indicate that the methods are scientifically valid methods. In this context, these alternative LLNA methods and the expanded applicability domain may result in additional data that could be used to make a determination of whether an undiluted chemical or a mixture is a "strong sensitizer."

There are inherent problems of testing of mixtures and formulations, and it applies across all toxicity test methods, not just the LLNA. The agency encourages ICCVAM to continue to accrue data, because the revised draft Addendum does not consider many classes of formulations to which humans may be exposed. On December 28, 2011, the Commission voted to approve the recommendation of ICCVAM regarding the LLNA with regard to its ability to determine the potency of a sensitizing substance. The Commission's recommendation is that the LLNA should not be considered a standalone assay for skin sensitization potency classification. However, based on the strength of the analysis provided and the currently available database of LLNA data, this assay can be a valuable tool in a weight-of-evidence evaluation for determining the skin sensitization potency of a substance. The agency also encouraged ICCVAM to continue to accrue data. Although the existing National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) database of LLNA test data is large (more than 600 substances), most of the available data consists of substances that are moderate, weak, or nonsensitizers, classes of substances that fall outside the CPSC's jurisdiction.

Currently, no *in vitro* or *in silico*[24] tests have been validated for determining skin sensitizing potential. Both approaches are evolving methodologies and are actively being pursued to reduce the number of laboratory and animal experiments performed. There are four *in vitro* test methods that are in pre-validation review in the European Union. It is expected that none of these methods, each relating to a specific mechanistic step occurring in skin sensitization, will be accepted as a stand-alone method and instead will be part of an integrated testing strategy. The validation of some of these *in vitro* methods may be completed in 2013. In addition, the European Commission and the European Centre for the Validation of Alternative Methods

[24] *In silico* data is a computational approach, using sophisticated computer models for the determination of a sensitizing potential, instead of use of animals or *in vitro* tests.

(ECVAM, the equivalent of ICCVAM in Europe) submitted a project proposal to the OECD in February 2012, regarding development of integrated testing strategies with the aim of replacing or reducing animal testing for skin sensitization. They will evaluate the four *in vitro* test methods above, along with nine other methods. Recent communications indicate that an integrated testing strategy for skin sensitization may not be available until 2017, due to the incorporation of the evaluation of potency of a skin sensitizer into the integrated strategy.

At this time, there are no validated *in vitro* or *in vivo* test methods for detecting and classifying respiratory sensitizers. There have been significant advances in the tools and methods available for hazard characterization of skin sensitizers, as discussed above; but progress has lagged for respiratory sensitizers. Because recognized and validated test methods are currently not available, identification of respiratory sensitizers is based on the induction of specific respiratory hypersensitivity response. Human evidence could consist of lung function tests supported by skin prick tests, serological analysis, and/or bronchial challenge tests (further discussion is found in the proposed Strong Sensitizer Guidance Document located in Appendix C). These tests should be complemented with medical history to support clinical relevance. Existing animal data can also be employed, although no standard animal model currently exists. Skin sensitization data can also aid in the determination of whether a substance is a strong respiratory sensitizer because many substances known to induce skin responses also induce respiratory responses.

Appendix C
CPSC Staff's Strong Sensitizer Guidance Document

For a product containing a strong sensitizer to be considered a hazardous substance and to require cautionary labeling under the FHSA,[25] 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.[26] 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.[27] Therefore, determining whether a cautionary label is required must occur on a product-by-product basis, and it is not based solely on the presence of a strong sensitizer in a product.

The designation of a substance as a "strong sensitizer" is a Commission-made determination. Once the Commission has designated a substance as a "strong sensitizer," CPSC staff believes that consideration of the "complexity of the mixture ("matrix")" is important in the risk characterization of a strong sensitizing chemical because 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 matrix components also can enhance the sensitizing capability of a substance in that mixture. For example, surfactants, a broad class of chemicals, are common in consumer products as processing agents and detergents. Surfactants like sodium lauryl sulfate are known to enhance the allergenicity of some chemicals. The Commission makes a decision to declare a substance a "strong sensitizer," but the risk characterization is based on the product as a whole. Risk characterization and risk management (*e.g.*, label, no label, or ban) would have to take into consideration the form in which the sensitizer is present in the actual product. A chemical matrix is the formulation in which the sensitizing agent is present.

If a substance containing a strong sensitizer is a hazardous substance under the FHSA, the product would require cautionary labeling, including the signal words: "Caution," or "Warning," and include an affirmative statement, such as: "May Produce Allergic Reaction by Skin Contact."[28] 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 appropriately and in accordance with FHSA requirements, a product that is intended or packaged in a form suitable for use in the household. However, if a toy or other article intended for use by children is or contains a hazardous substance that a child could access, the product, by definition, is a banned hazardous substance, unless specifically exempted.[29]

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[25]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.

[26]16 C.F.R. §1500.3(b)(4)(i)(A).

[27] The term "substance" for strong sensitizers can mean both the chemical and products containing the chemical. For example, "paraphenylenediamine and products containing it," are listed as meeting the definition for "strong sensitizer" in FHSA section 1500.13, "Listing of `strong sensitizer' substances."

[28] 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*.

[29]15 U.S.C. §1261(f)(1(A); id. §1261(q)(1).

The following sections of this guidance document take a stepwise approach in clarifying each component of the strong sensitizer supplemental definition. Each section incorporates the current science rationale behind potential decision making. These guidelines are intended to aid manufacturers and other stakeholders in understanding how CPSC staff would assess whether a substance could be considered a "strong sensitizer." The following sections quote the relevant part of the definition and provide guidance concerning that part of the definition.

I. Sensitizer

Sensitizer. A sensitizer is a substance that is capable of inducing 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 reexposure to the same substance.[30]

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 (Types I, II, III and IV), representing four different mechanisms leading to the body's response to the allergens. For hypersensitivity Types I, II and III, exposure to an allergen results in the production of specific antibodies (*e.g.*, Immunoglobulin M [IgM], IgG or IgE). Some substances may not have defined specific IgE responses but exhibit other immunologically mediated characteristics of sensitizers. Therefore, these substances can be classified as sensitizers, based upon the other characteristics.[31] Allergic responses typically 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.

Due to the nature of the immune system, in order for an individual to become sensitized to a particular substance, there is a lag sensitization phase (induction), followed by a secondary immune response (elicitation phase). The amount of time and the amount of exposure (the variable period of exposure and the dose) required for sensitization will depend upon the individual.[32] In the scientific community, it is generally considered that time is required for sensitization to develop; it is unusual, although not impossible, for simultaneous sensitization and elicitation to occur upon first exposure. Because of the latent period, the first contact (and often repeated contacts), even with relatively high concentrations of a sensitizer, can go undetected because no signs or symptoms of allergy occur. Individuals who are sensitized, but who 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 can have a stronger than expected response.

[30] Updated strong sensitizer supplemental definition 16 C.F.R. §1500.3(c)(5).
[31] The production of IgE antibodies is typical of Type I hypersensitivity reactions (*e.g.*, rhinitis, urticaria).
[32] It typically takes 7 to 14 days for an immune response to develop.

It is important to distinguish a "sensitizer" response from what could be an "irritant response."[33] Irritant responses occur without sensitization. An irritant is any agent that is capable of producing cell damage and/or an inflammatory response 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. Irritant symptoms can occur within minutes of 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. Allergic responses (*e.g.*, allergic contact dermatitis) can be localized but may also have widespread skin involvement, particularly in patients with strong sensitization.

In the future, with progress in the science, a definition for each functional class of allergen (*e.g.*, protein, chemical) or target organ (*e.g.*, respiratory, ocular, skin) may be necessary. However, at this time, insufficient evidence exists to separate clearly the sensitization characteristics (*e.g.*, mechanisms of sensitization) of the different target organs.

II. Significant Potential for 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 hypersensitivity 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.[34]

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:

(A) well-conducted clinical and diagnostic studies;
(B) epidemiological studies, with a preference for general population studies over occupational studies;
(C) well-conducted animal studies;
(D) well-conducted *in vitro* test studies;
(E) cross-reactivity data;

[33] 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.
[34] Updated strong sensitizer supplemental definition 16 C.F.R. §1500.3(c)(5).

(F) case histories.

A. Considerations Used by CPSC Staff:

The determination of the significant potential for causing hypersensitivity is the cornerstone of the definition of "strong sensitizer." The determination of risk of hypersensitivity should follow a weight-of-evidence approach, using 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. The factors for consideration of hypersensitivity potential are ranked and listed in order of importance in the definition, with the FHSA preference for human data over animal data. Occupational studies are considered a subset of epidemiological studies. Epidemiological studies (general population studies) are preferred over occupational studies because the general population is of concern to the CPSC, and 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. Although providing helpful information regarding the potential sensitizing strength of a chemical, occupational data could exaggerate the estimation of the sensitizing strength of a chemical to the consumer scenario. If population data are lacking, worker sensitization prevalence could be used to estimate prevalence in the exposed general population by taking exposure and dose-response relationships into account. "Case histories" are studies typically on a single individual and are less helpful in providing information on sensitization in the general population.

CPSC staff, when evaluating existing data from human and/or animal studies, takes the quality of the data into consideration.[35] Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration and use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP), and good epidemiological practice (GEP).

1. Respiratory Sensitization:
   At this time, there are no validated *in vitro* or *in vivo* test methods for detecting and classifying respiratory sensitizers. There have been significant advances in the tools and methods available for hazard characterization of skin sensitizers, as discussed below; but progress has lagged for respiratory sensitizers. Because recognized and validated test methods currently are not available, identification of respiratory sensitizers is based on the induction of

[35] Neither the FHSA, nor the Commission's regulations *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to a minimum number of animals, and the policy also advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. In making the appropriate hazard determinations, manufacturers of products subject to the FHSA, should use existing alternatives to animal testing whenever possible. These include prior human experience, literature sources that record results of prior animal testing or limited human tests, and expert opinion. Recommended procedures can be accessed on the Commission's Web page at: http://www.cpsc.gov/BUSINFO/animaltesting.html.

specific respiratory hypersensitivity. Human evidence could consist of lung function tests supported by skin prick tests, serological analysis, and/or bronchial challenge tests. These tests should be complemented with medical history to support clinical relevance. Existing animal data can also be employed, although no standard animal respiratory hypersensitivity model exists. Skin sensitization data can also aid in the determination of whether a substance is a strong respiratory sensitizer because many substances known to induce skin responses also induce respiratory responses.

2. Skin Sensitization:
Historically, data on the skin sensitization potential of chemicals came from studies using human volunteers. Two tests for predicting whether a person will become sensitized to a substance are the Human Maximization Test (HMT) and the Human Repeat Insult Patch Tests (HRIPT).[36] The HMT is no longer in use, due to ethical concerns about its potential to create adverse health consequences for the person being tested. Contract laboratories have performed the vast majority of human sensitization tests, particularly the HRIPT. There are a limited number of scientific publications with human sensitization data, of which much is derived from older studies.

Prior to development of the Local Lymph Node Assay (LLNA), the Guinea Pig Maximization Test (GPMT) and the Buehler Assay (BA) had been the primary animal assays used to determine the skin sensitizing ability of a chemical. The GPMT is a highly sensitive method; however, some of the sensitivity arises due to the coadministration of a painful immune stimulant. This method involves injecting under the skin of the animal the possible sensitizer being tested, as well as applying it to the surface of the skin. The BA uses repeat closed topical applications (filter papers containing the test sensitizer of interest are covered with a patch and taped to the skin in order to enhance absorption of the substance). The GPMT is regarded as a more sensitive assay that, for certain substances, also may overestimate the sensitization hazard for the compound tested. The BA is less sensitive and may underestimate the sensitization potential of a compound.

In 1997, the LLNA was proposed by the test method developers to ICCVAM as a standalone alternative method to the GPMT and the BA for skin sensitization hazard identification.[37] In 1999, based on the validation database and performance of the test method, the LLNA was recommended by ICCVAM as an alternative test method for assessing the skin sensitization potential of most types of substances. The consensus of the ICCVAM scientific peer review panel was that the LLNA performed as well as the

[36] These tests vary with regard to the number of induction patch tests, the placing of the patches, and the use of a maximization step (an amplifying step during the challenge phase, this step involves co-treatment of the test sensitizer of interest with an irritant in order to enhance a potential response).
[37] The LLNA provides a yes/no answer about whether a substance is a sensitizer.

GPMT and BA for hazard identification of strong-to-moderate chemical sensitizing [dermal] agents but lacked strength in predicting accurately some weak sensitizers and some strong irritants. The LLNA provides several advantages compared to the guinea pig assays, including elimination of potential pain and distress, use of fewer animals, shorter test duration, a more objective end point, less test substance required, and the availability of dose-response information. U.S. regulatory agencies (including the CPSC) accepted the LLNA as a valid alternative test method for allergic contact dermatitis testing. The LLNA was adopted as a test guideline (test guideline [TG] 429) in 2002, by the Organization for Economic and Cooperative Development (OECD).

On March 9, 2010, the Commission voted unanimously to approve ICCVAM recommendations including: (1) updates to the test method protocol; (2) establishment of performance standards; and (3) a modified form of the assay, the reduced Local Lymph Node Assay (rLLNA). The revised LLNA test method protocol and the LLNA performance standards encourage the reduction, refinement, or replacement of animals in testing. On January 26, 2011, the Commission voted to approve the recommendations of ICCVAM regarding an expanded applicability domain and two nonradioactive versions of the LLNA: (1) the Bromodeoxyuridine Enzyme-linked Immunosorbent Assay (BrdU-ELISA); (2) the Daicel Chemical Industries version (LLNA:DA), which have been adopted by the OECD, as Test Guideline 442B and Test Guideline 442A, respectively. These alternative, nonradioactive LLNA test method protocols encourage the reduction, refinement, or replacement of animals in testing, and the data indicate that the methods are scientifically valid methods. In this context, these alternative LLNA methods and the expanded applicability domain may result in additional data that could be used to make a determination of whether an undiluted chemical or a mixture is a "strong sensitizer."

There are inherent problems with testing of mixtures and formulations, and this applies across all toxicity test methods, not just the LLNA. The agency encourages ICCVAM to continue to accrue data, because the ICCVAM revised addendum on the applicability domain for the LLNA does not consider many classes of formulations to which humans may be exposed. On December 28, 2011, the Commission voted to approve the recommendation of ICCVAM regarding the LLNA with regard to its ability to determine the potency of a sensitizing substance. Staff's recommendation is that the LLNA should not be considered a standalone assay for skin sensitization potency classification. However, based on the strength of the analysis provided and the currently available database of LLNA data, this assay can be a valuable tool in a weight-of-evidence evaluation for determining the skin sensitization potency of a substance. The agency also encouraged ICCVAM to continue to accrue data. Although the existing National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

database of LLNA test data is large (more than 600 substances), most of the available data consists of substances that are moderate, weak, or nonsensitizers, classes of substances that fall outside the CPSC's jurisdiction.

There are strengths and weaknesses with each of the aforementioned assays; however, CPSC staff believes that all could be used in a weight-of-evidence evaluation under the FHSA.

Currently, no *in vitro* or *in silico*[38] systems have undergone validation for determining skin sensitizing potential. Both approaches are evolving methodologies and are actively being pursued to reduce the number of expensive laboratory and animal experiments performed. Multiple *in vitro* test methods for skin sensitization are in pre-validation review. CPSC staff expects that none of these methods, each relating to a specific mechanistic step occurring in skin sensitization, will be accepted as a standalone method and instead will be part of an integrated testing strategy. The validation of some of these *in vitro* methods may be completed in the next couple of years. CPSC staff expects that an integrated testing strategy for skin sensitization may be available within the next 5 years.

3. Other Factors:
CSPC staff considers the term "non-sensitized" to be an appropriate term for what would be considered the control general population because it includes both non-exposed individuals and exposed individuals who are not sensitized to the allergens.

There is a complex relationship among the following: 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 percent greater chance of having at least one child with asthma.[39] 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.[40] The incidence of asthma has risen dramatically in the past 20 years; the number of asthma cases in the United States for all age groups has increased by at least 75 percent over the

[38] *In silico* data is a computational approach, using sophisticated computer models for the determination of a sensitizing potential.
[39] 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.
[40] 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.

past 2 decades, while the rate among children under the age of 5 has increased more than 160 percent, and it continues to rise.[41] This is 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.

Differences may exist between susceptibility to respiratory allergens and to 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, ethylenediamine, thimerosal, merbromlin (mercurochrome), balsam of Peru, rubber chemicals in shoes, and poison ivy.[42] More research is necessary to determine whether these differences between susceptibility to respiratory allergens and skin allergens exist.

Currently, there is conflicting data to determine age-specific susceptibility to skin allergens; however, this may change as more information becomes available because 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 increased more than 300 percent since the 1960s.[43] 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." CPSC staff will consider susceptibility qualifiers (*e.g.*, genetics, age, gender, and atopic status) in their evaluation of the potential of a substance to cause significant hypersensitivity.

> *Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), in silico data, specific human sensitization threshold values, other data on potency and sensitizer bioavailability, if data is available and the methods validated. 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*

[41] 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; Akinbami et al., NCHS Data Brief 2012, No.94, "*Trends in Asthma Prevalence, Health Care Use, and Mortality in the United States, 2001−2010.*

[42] Fisher's Contact Dermatitis, 2001, 5th edition, Rietschel RL and Fowler J, eds. Lippincott, Williams and Wilkins, New York.

[43] American Academy of Allergy Asthma and Immunology (AAAAI), Allergy Statistics, Media Kit; and, Horan RF et al., JAMA 1992, 268: 2858-68; Atheron et.al. Community Practioner 2005, 78(7): 255−257; Matiz et.al. Giornale Italiano di Dermatologia E Venerologia 144(5): 541−546; Smith et.al. Pediatr Dermatol 2009, 26(3): 369−370; Thyssen et.al. Contact Dermatitis 2007, 57: 287−299.

absorb the allergen and the actual penetrating ability of the allergen, including such factors as size and composition of the chemical.

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 and *in silico* approaches are evolving methodologies that have not been validated yet; but CPSC staff believes that they may be useful and may be used as part of a weight-of-evidence approach and/or in an integrated testing strategy. These techniques are being pursued to reduce the numbers of expensive laboratory (*in vitro*) and animal (*in vivo*) experiments carried out.

B. Frequency of Occurrence and Severity of Reaction

Before the Commission designates any substance as a "strong" sensitizer, frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility 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. A clinically important reaction would be considered one with a 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. 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*[44]

The classification of a strong sensitizer under the FHSA is complex. As indicated by the statutory definition, careful consideration of the prevalence of sensitization (frequency of occurrence) and severity of response should be carried out in addition to evaluating a substance's potential to cause sensitization in designating a substance as a strong sensitizer. Each component needs to be weighed in light of other available data. For example, a substance may be a common sensitizer due to widespread exposure to the general population; however, the reactions to exposure to the substance may be mild and the sensitizing strength (potency) low. Therefore, such a substance may not be designated a strong sensitizer even though it has a higher frequency of occurrence.

Data for the determination of a sensitization frequency cut-off limit, a tolerable level of sensitization/allergy prevalence, for the general population is limited because most epidemiological studies are performed on a subset of the general population, that is, on individuals who are already sensitized. Data are available on several chemicals that could serve as a template in deriving a frequency-of-occurrence limit; however, these

[44] Updated strong sensitizer supplemental definition 16 C.F.R. §1500.3(c)(5).

chemicals are predominantly occupational sensitizers. Because the degree of sensitization in the workplace can be greater than that of the general population, due to greater exposure (both in time, concentration and product use) to the sensitizing agent, CPSC staff believes that caution should be employed in applying 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; yet the prevalence for the general population is estimated to be below 1 percent.[45] However, sensitization in the workplace can serve as a harbinger for consumer sensitization, as observed with the preservative MCI/MI,[46] which was known as a workplace allergen when it first came into use. Since then, it has risen to be among the top 30 of allergic contact dermatitis allergens for the general population of North America.

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) indicated that 20 percent of the general population will develop an allergy-related illness (sinusitis, rhinitis, bronchitis, asthma).[47] However, with the rate of allergy in industrialized countries increasing dramatically over the past 2 decades, and with prevalence factors likely varying for each sensitizing agent, setting a sensitization frequency cut-off limit for a "strong sensitizer" at 1 percent may be overly protective or insufficiently protective. CPSC staff believes that identifying a substance as a "strong sensitizer" based on a sensitization frequency cut-off rate value is best considered on a case-by-case, weight-of-evidence criteria, if sufficient data are available.

In the following section, CSPC staff discusses specific objective criteria for evaluating the severity of a reaction in the respiratory system and skin, to bring objectivity to an area of great subjectivity, by providing clinically sound and reproducible criteria for defining levels of impairment.

1. Determining the Severity of Respiratory and Skin Sensitization Responses

a. <u>Respiratory</u>

Airway hyper-responsiveness (AHR) is a characteristic feature of the lungs of asthmatic individuals, although AHR also can be found in individuals with non-allergic conditions of airflow obstruction (*e.g.*, chronic obstructive pulmonary disease). Inhaled stimuli, such as environmental allergens, can increase airway inflammation and enhance AHR. Changes in AHR can be

[45] 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.
[46] MCI/MI: methylchloroisothiasolinone/methylisothiasolinone; Pratt et al, Dermatitis 2004, 15(4): 176−183.
[47] IOM (Institute of Medicine), 1993. *Indoor Allergens: Assessing and Controlling Adverse Health Effects.* Washington DC, National Academy Press.

smaller in healthy subjects than those measured in asthmatic patients with persistent AHR; they are similar to the changes occurring in asthmatic patients with worsening asthma control. Therefore, measurements of AHR 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 nonspecific tests are used frequently in making a diagnosis and can be performed quickly, safely, and reproducibly in a clinical or laboratory setting.

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.[48] These guidelines suggest that asthma severity should 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,[49] these guidelines are in line with the American Medical Association's (AMA) respiratory impairment guidelines and tests recommended by the IOM.

Tests of pulmonary function (particularly FEV_1 and PEF measurements),[50] are considered the most useful, and they 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 "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.

[48] 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.

[49] 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

[50] FEV (forced expiratory volume) and PEF (peak expiratory flow)

CPSC staff believes that the classification categories, "moderate persistent" and "severe persistent" should be considered "severe" responses, in line with the FHSA "strong sensitizer" supplemental definition.

	Symptoms	Nighttime Symptoms	Lung Function	Medications[51]
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.
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.
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.
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.

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

[51] Short-term therapy is the same for each of the four NAEPP classification groups: short-acting $beta_2$ 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.

b. Skin

Allergic contact dermatitis is characterized by erythematous macules (discolored spots) and papules (circumscribed solid elevated areas on the skin with no visible fluid, which usually precedes vesicle and pustule formation), edema, fluid-filled vesicles, or bullae (blisters), 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 there is 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.[52]

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) that provide the best basis for making clinical decisions and severity scoring.[53] Three systems were considered to assess severity: W-AZS, Emerson et al[54] and IGADA (Investigator Global Atopic Dermatitis Assessment).[55] These systems use some or all of the above-mentioned criteria. CSPC staff suggests using a simplified version of the W-AZS severity scoring system[56] 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. CPSC staff would generally consider a severity score totaling from 99 points to 152 points to be "moderately severe" and a severity score of 153 or more to be "severe."

[52] Charman CR et al., Arch Dermatol 2005 Sep; 141:1146-51.
[53] Williams HC, NEJM 2005 June; 352(22):2314-24.
[54] Emerson RM et al., Br J Derm 2000; 142:288-97; who adapted the Rajka & Langeland index, an index that has been widely used as the basis for some of the more common severity scoring systems. This adaptation is simple and has been used 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.
[55] 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.
[56] Silny W et al., Acta Dermatov Croat 2005; 3(4):219-24.

Severity Index Score = I + II[57]

- **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 — **D: Severity signs of inflammation**

Body areas:			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

[57] Based on the W-AZS severity scoring system.

III. 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.[58]

In the future, with progress in the science, there may be a need to have a definition for classes of allergen (*e.g.*, chemical, protein, respiratory, ocular, skin). At this time insufficient evidence exists to clearly separate the sensitization characteristics (*e.g.*, different mechanisms of sensitization) of the different target organs.

Conclusion

Multiple considerations would be used by CPSC staff before suggesting that a substance is a strong sensitizer. The determination of risk of hypersensitivity should follow a weight-of-evidence approach, using all available validated tools. Existing human data are preferred over animal data. CPSC staff, when evaluating existing data from human and/or animal studies, takes the quality of the data into consideration. The frequency of sensitization occurrence and the severity of the sensitization response will be considered.

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.

Once designated as a strong sensitizer, for a product to be considered a hazardous substance and to require cautionary labeling under the FHSA, 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. 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, determining whether a cautionary label is required must occur on a product-by-product basis and is not solely based upon the presence of a strong sensitizer in a product.

[58] Updated strong sensitizer supplemental definition 16 CFR §1500.3(c)(5).

TAB B: Office of Compliance Staff Memo

TAB B

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

This document has been electronically approved and signed.

Memorandum

Date: February 13, 2013

TO: Joanna M. Matheson, Ph.D., Toxicologist, Directorate for Health Sciences

THROUGH: Marc Schoem, Acting Director, Office of Compliance and Field Operations
Mary Toro, Director, Division of Regulatory Enforcement, Office of Compliance and Field Operations

FROM: Carol Afflerbach, Senior Compliance Officer, Office of Compliance and Field Operations

SUBJECT: Proposed Update to the Strong Sensitizer Supplemental Definition and Proposed Strong Sensitizer Guidance Document

CPSC staff is preparing a package for Commission consideration to update the supplemental definition of "strong sensitizer" at 16 C.F.R. §1500.3(c)(5). In addition, staff has proposed guidance that describes the factors CPSC staff would consider when evaluating a substance for its potential as a strong sensitizer.

This memorandum provides the Office of Compliance and Field Operations (Compliance) recommendations regarding the Proposed Update to the Strong Sensitizer Supplemental Definition and Proposed Strong Sensitizer Guidance Document.

Background:

The Federal Hazardous Substance Act (FHSA), 15 U.S.C. 1261−1278, was enacted on July 12, 1960. Included within the Act's definition of hazardous substance is "strong sensitizer." 15 U.S.C. §1261(f)(1)(iv). Section 2(k) of the FHSA, defines "strong sensitizer" as:

> A substance which will cause on normal living tissue through an allergic or photodynamic 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 a significant potential for causing hypersensitivity.

On August 12, 1961, the U.S. Food and Drug Administration, which, at that time, administered the FHSA, issued regulations under the FHSA that supplemented the statutory definition of "strong sensitizer." 26 FR 7334. In 1973, the responsibility for the administration of the FHSA was transferred to the U.S. Consumer Product Safety Commission and the supplementary definition of "strong sensitizer," referred to above, was published at 16 C.F.R. §1500.3(c)(5).

The supplemental definition explained further the various terms used in the statutory definition. Advances in understanding the basic principles involved in allergic hypersensitivity and immunology indicated that the previous supplemental definition was incorrect in at least two respects. On May 30, 1984, the supplementary definition published in 1961 was revoked.

In September 1984, the Commission established the Technical Advisory Panel on Allergic Sensitization to assist staff in developing appropriate terms and criteria for a supplemental definition of "strong sensitizer" that would reflect current scientific theory. On November 7, 1985, the Commission proposed the supplemental definition for "strong sensitizers." No comments were received on the proposal.

On August 14, 1986, the Commission issued a final rule supplementing the definition of "strong sensitizer" in the FHSA. The supplementary definition clarified how the statutory definition should be interpreted in view of then-current scientific knowledge, and the definition explained the factors that the Commission would consider in determining whether a substance, or any product containing such substance, is a strong sensitizer.

Discussion:

CPSC staff recommends that the Commission publish a proposed rule revising the supplemental definition for strong sensitizer to align with current science, based on advances in understanding the basic principles involved in allergic hypersensitivity mechanisms. In addition, the revisions to the supplemental definition will harmonize the definition of "strong sensitizer" with other classification systems. The proposed changes to the supplemental definition are more objective, eliminate redundancy and subjective factors, incorporate new technology, rank the criteria for classification of strong sensitizers in order of importance, define criteria for "severity of reaction," and indicate that a weight-of-evidence approach will be used. Staff also has developed a guidance document that provides well-defined criteria that CPSC staff would consider when evaluating whether a substance is a strong sensitizer.

Staff believes that the proposed strong sensitizer guidance document takes a stepwise approach in clarifying each section of the strong sensitizer supplemental definition. Each section incorporates the current science rationale behind the potential decision making. The document should assist manufacturers and other stakeholders in understanding how CPSC staff would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer." These clarifications could reduce unnecessary or expensive testing performed by manufacturers and should not place any additional cost burdens on the industry.

Even where a chemical is determined to be a strong sensitizer, section 2(f)(1)(A) of the FHSA requires that in order for a strong sensitizer to be a hazardous substance, it must be capable of causing "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." 15 U.S.C. §1261(f)(1)(A).

Conclusion:

The draft proposed supplemental definition is consistent with the methodology of the Globally Harmonized System of Classification and Labeling of Hazardous Chemicals and will assist manufacturers in understanding how CPSC staff and the Commission would assess whether a substance and/or product containing that substance could be considered a "strong sensitizer." Compliance staff agrees that the supplemental definition of "strong sensitizer" should be aligned with current science and updated.

Compliance staff agrees that the proposed supplemental definition and the guidance document give clear guidance to stakeholders regarding the factors the Commission staff will consider when evaluating whether a substance is a strong sensitizer. Additionally, the guidance document can be updated, when necessary, to stay consistent with current practices, without having to change the supplemental definition. We believe that this will lead to efficient administration of the Act and enforcement of the regulation.

TAB C: Directorate for Economic Analysis Staff Memo

TAB C

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

This document has been electronically approved and signed.

Memorandum

Date: February 13, 2013

TO : Joanna M. Matheson, Toxicologist, Directorate for Health Sciences

THROUGH: Gregory B. Rodgers, AED, Directorate for Economic Analysis

Deborah V. Aiken, Senior Staff Coordinator, Directorate for Economic Analysis

FROM : Robert Franklin, Economist, Directorate for Economic Analysis

SUBJECT : Draft Proposed Rule Revising the Definition of "Strong Sensitizer": Assessment of Potential Impact on Small Entities

CPSC staff is recommending that the Commission propose a rule that would update or amend the supplemental regulatory definition of "strong sensitizer." The regulatory definition of "strong sensitizer," which is found at 16 C.F.R. §1500.3(c)(5), is intended to interpret or supplement the statutory definition, which is restated at 16 C.F.R. §1500.3(a)(9). This memorandum discusses the potential impact of the draft proposed rule on small entities.

Background

Under the Federal Hazardous Substances Act (FHSA), a substance that is a strong sensitizer is considered a *hazardous substance* if it may cause "substantial personal injury or substantial personal illness" as a result of its "reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." Under the FHSA, products that are hazardous substances are required to bear warning labels, except in the case of children's products, in which case the product is banned.

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

In order to interpret and supplement the statutory definition of "strong sensitizer," the Commission promulgated a supplemental regulatory definition of "strong sensitizer" (16 C.F.R.

§1500.3(c)(5)). This regulatory definition is intended to provide the public with a better understanding of how the Commission interprets the terms in the statutory definition, including what it will consider in determining that a substance that is a sensitizer is a "strong" sensitizer. It is this regulatory definition of "strong sensitizer," for which the draft proposed rule would modify.

A manufacturer does not need to label a product as being or containing a strong sensitizer until the Commission has designated the substance a strong sensitizer. This is done through a separate rulemaking procedure. To date, only five substances have been designated to be strong sensitizers.[59] These designations all were made prior to the establishment of the CPSC, when the administration of the FHSA was the responsibility of the U.S. Food and Drug Administration.

Reasons for the Recommended Changes to the Regulatory Definition

The recommended changes to the regulatory definition of "strong sensitizer" are discussed in detail in a CPSC Memorandum from Joanna M. Matheson.[60] The recommended changes to the regulatory definition of "strong sensitizer" are intended to make the definition more consistent with current scientific knowledge and to describe better the criteria that the Commission will use to determine whether a substance is a strong sensitizer. The changes should also make the regulatory definition more consistent with the Globally Harmonized System of Classification and Labeling of Chemicals, which is intended to make various systems in different countries for classifying and communicating the hazards associated with chemicals more consistent with each other. Among the recommended changes are ones that are intended to make better distinctions between substances that are irritants and that are sensitizers, to state that a "weight of evidence" approach will be used in making a determination that a substance is a strong sensitizer, and to allow for the use of techniques for evaluating the sensitizing potential of substances that are under development and are expected to be validated in the near future.

Potential Impact on Small Entities

The draft proposed rule would amend the supplemental regulatory definition of "strong sensitizer," essentially updating the definition to make it more consistent with current scientific understanding of sensitization and to make it more consistent with the Globally Harmonized System of Classification and Labeling of Chemicals. The purpose of the supplemental regulatory definition is to interpret the statutory definition of "strong sensitizer" and to provide the public with a better understanding of how the Commission interprets the terms in the statutory definition, including what it will consider in determining whether a substance is a strong sensitizer.

[59] These substances are listed at 16 C.F.R. §1500.13.

[60] Consumer Product Safety Commission (February 13, 2013) – "Proposed Update to the Strong Sensitizer Supplemental Definition and Proposed Strong Sensitizer Guidance Document," Memorandum from Joanna M. Matheson, Directorate for Health Sciences, to the Commission.

Amending the supplemental regulatory definition of "strong sensitizer" will not impose any direct burden on any small business or other entity. The Commission actually must designate a substance as a strong sensitizer, which is done through a separate rulemaking procedure, and the product would have to meet the FHSA definition of a "hazardous substance" before manufacturers would be required to add the necessary warning labels to products that contain the substance. Moreover, the amendments recommended by CPSC staff are not expected to impose any indirect burden on small businesses or other entities because they are not expected to lead to any additional substances being designated as strong sensitizers that would not be so designated in the absence of the amendments. Therefore, the Commission can certify that the draft proposed rule amending the supplemental regulatory definition of "strong sensitizer" will not have a significant impact on a substantial number of small entities.

Environmental Impact

The National Environmental Policy Act requires that the Commission consider the impact of its actions on the environment. The draft proposed rule would only amend the definition of "strong sensitizer" and would not require any actions on the part of manufacturers or other parties that could impact the environment. Generally, CPSC rules are considered to "have little or no potential for affecting the human environment," and environmental assessments and environmental impact statements are not usually prepared for these rules (see 16 C.F.R. §1021.5(c)(1)). The Commission does not expect the rule to have any adverse impact on the environment under this categorical exclusion.

TAB D: March 2008 CPSC Staff "Strong Sensitizer" Supplemental Definition Technical Report

TAB D

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

Joanna M. Matheson
March 13, 2008

Phone: 301-504-7043
E-mail: jmatheson@cpsc.gov

This report already proceeded through clearance. It is included in the briefing package for easy reference.

**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.*

Table of Contents

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 C.F.R. §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.[61] 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 to 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, held expert consultation on current issues in skin sensitization risk assessment in February 2007 and March 2008 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 U.S. Food and Drug Administration (FDA) until it was transferred to the 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) and is restated in 16 C.F.R. §1500.3(b)(9)) states:

[61] C.F.R. §1500.3(c)(5).

**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.*

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 FDA identified five substances as strong sensitizers[62]:

- 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; and
- oil of bergamot and products containing 2 percent or more of oil of Bergamot

Since its inception in 1972, the 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).[63] 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*

[62] 16 C.F.R. §1500.13.

[63] 16 C.F.R. §1500.3(c)(5).

- *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*

- 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,[64] the

[64]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.

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.[65] 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.[66] 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.[67]

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.*[68] 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.[69]

[65]16 C.F.R. §1500.3(b)(4)(i)(A).
[66] 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*.
[67]16 C.F.R. §1500.3(b)(15)(i).
[68]16 C.F.R. §1500.14(b)(8)(i)(B)(9).
[69]16 C.F.R. §1500.14(b)(8)(i)(E)(5).

B. Globally Harmonized System of Classification and Labeling of Chemicals (GHS)[70]

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: "*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: "*the GHS does not include establishment of uniform test methods or promotion of further testing to address adverse health effects*." The last parameter stated: "*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[71]: (1) the identification of relevant data, (2) the review of that data, and (3) 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: "*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*

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

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: "*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.*[72] *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) that frequently accompany respiratory hypersensitivity.

The GHS provides additional 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*[73]*); 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 standalone 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 of 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

[72] Rhinitis is inflammation of the nasal mucosa and conjunctivitis is inflammation of the conjunctiva, the membrane that 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.

[73] 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.

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 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*[74] *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.[75] Generally, the greater the level of exposure (*i.e*., dose), the more vigorous will be the induced immune response. Furthermore, the greater the sensitization of an individual to a particular substance, the less dose of the allergen needed to induce a hypersensitivity response. CPSC staff recognizes that there are exceptions to this general statement: inter-individual differences in response and susceptibility; exposure conditions (*e.g*., presence of a solvent that enhances penetration) can impact on a chemical's sensitizing ability. While doses massively above an optimal immunizing dose with some chemicals can result in tolerance to these chemicals, other high exposures, such as occupational exposures involving large chemical spills (*e.g*., isocyanates) have demonstrated the ability of chemicals to sensitize. In addition to dose, the ability of a chemical to cause sensitization also can be linked to its physico-chemical properties (*e.g*., skin-penetrating capacity, ability to bind skin proteins).

[74] 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).
[75] Kimber I et al,Toxicological Sciences 2001, 59:198−208.

These qualities of dose and a chemical's properties help determine the chemical's "potency" as a sensitizer or allergen.[76]

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: "*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*."

The OECD Task Force for Classification and Labeling in its OECD Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures, Chapter 2.4 Appendix, includes a two-category system for classifying sensitizers. Category 1 defines "strong sensitizer," and Category 2 defines "low-to-moderate sensitizers."

A 2002 United Nations (UN) mandate[77] directed the OECD to consider use of "strong versus weak" sensitizers in the GHS. This mandate was extended for the 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 from a group of European constituents is to consider a multiclass 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 using either animal data or human data be determined in relation to the requirements of the GHS, which is based on hazard classification.[78]

[76] The National Library of Medicine defines "potency" as the relative toxicity of an agent as compared to a given or implied standard or reference.
[77] ST/SG/AC.10/C.4/2002/19, December 2002, UN Subcommittee HCL.
[78] OECD Scientific Issue Paper on Strong vs. Weak Sensitizers, May 24, 2006; OECD.

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

A scientific panel was convened by CPSC staff in 2004−2005, to address the definition of *"strong sensitizer"* that appears in section 2(k) of the Federal Hazardous Substances Act (restated in 16 C.F.R. §1500.3(b)(9)) and supplemented in §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 (Centers for Disease Control and Prevention, 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 supplemental definition of "strong sensitizer," 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 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 that CPSC staff had 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 multiclass categorization for chemical sensitizers based upon potency (*e.g*., weak, moderate, strong, and extreme). Therefore, the second question CPSC asked the panel to consider was whether additional classification categories should be incorporated into the FHSA definition of a "sensitizer." The last three questions the CPSC presented to the panelists concerned ongoing issues in the field of immunotoxicology with regard to

sensitization (*i.e.*, validated and appropriate tests for identifying sensitizing substances, children as a susceptible population, and chemical matrix effects[79]). The responses to the last three questions are relevant for CPSC staff's risk assessment of sensitization after 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 meeting of July 21 and the written responses submitted by the panelists to staff's questions. A summary of the panel discussion is preceded by the specific question in bold face type; CPSC staff's 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.

Panel Discussion

Each panel member recommended that the definition be revised, although 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 CSPC staff discussion and 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 using a more classical definition incorporating the stages of the sensitizing process:

[79] 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.

> "*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 of 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 because 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 and also consider the GHS definitions. Therefore, the panel began the 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 considered sufficiently in the GHS definition. Furthermore, they noted that the GHS does not consider severity of reaction.

Because 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.

CSPC Staff Discussion and 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, and CPSC staff agreed, that more specific, and, if available, more quantitative criteria be provided to illustrate what designates a sensitizer as "strong" versus "weak." The determination of what is a strong sensitizer can only be made in the context of a comparison because the intent of the FHSA is to address only

a subset of sensitizers, those having a significant health impact. One panelist suggested dropping the word "strong" and using a more classical definition incorporating the stages of the sensitizing process. The other panelists did not agree with this suggestion, and CPSC staff does not agree with the suggestion either. The FHSA supplemental definition (*i*) for "sensitizer" reflects 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 unnecessarily to be sensitizers would increase dramatically, as would the number of products that could require labeling unnecessarily.

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 expressed the belief that the FHSA definition was more comprehensive than GHS's definition. The classification of a strong sensitizer under the FHSA is complex. As defined by the statutory definition, careful consideration of the prevalence of sensitization (frequency of occurrence) and severity of response should be carried out in addition to an evaluation of a substance's potential to cause sensitization in determining whether to declare a substance to be a strong sensitizer. Each component needs to be weighed in light of other available data. For example, a substance may be a common sensitizer due to widespread exposure to the general population. However, the reactions to exposure to the substance may be mild and the sensitizing strength (potency) low. Therefore, such a substance may not be designated as a strong sensitizer, even though it has a higher frequency of occurrence.

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 they do exhibit the other immunologically-mediated characteristics of sensitizers, and therefore, these substances are classified as sensitizers

based upon these other characteristics.[80] 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 because insufficient evidence exists to separate clearly 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*) to avoid the implication that "sensitizer" includes what could be an "irritant response."[81] 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 fit more appropriately 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.

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

[81] 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.

CSPC Staff Discussion and Summary

CPSC staff concurs with the panelists' recommendation not to define further the term "immunologically-mediated." Trying to define "immunologically-mediated" further would create the potential for exclusion of substances that sensitize through atypical mechanisms. However, the weight-of-evidence approach suggested by CPSC staff should ensure that these substances will be captured in the assessment process.

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

The panelists' focus on the presence/absence of an IgE response is that the immune mechanism most commonly associated with a respiratory allergic response is the presence of specific IgE antibodies to the allergenic substance.[82] 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. In addition, specifying an antibody-mediated mechanism is not applicable to many dermal sensitizing substances. Allergic contact dermatitis is not antibody-mediated; it is mediated by chemical-specific T lymphocytes.

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. Due to the nature of the immune system, in order for an individual to become sensitized to a particular substance, there is a lag sensitization phase (induction), followed by a secondary immune response (elicitation phase). The amount of time and the amount of exposure (the dose) required for sensitization will depend upon the individual.[83] In the scientific community, it is generally recognized that it takes time for sensitization to develop; it is unusual for simultaneous sensitization and elicitation to occur upon first exposure. Because of the latent period, the first contact (and often repeated contacts), even with relatively high concentrations of a sensitizer, can go undetected because no signs or symptoms of allergy occur. Individuals who are sensitized but do not exhibit clinically detectable sensitization (*i.e.*, do not exhibit symptoms) when challenged

[82] 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.

[83] It typically takes 7 to 14 days for an immune response to develop.

are characterized as having “subclinical sensitization.” When challenged a second time in a clinical setting, these individuals can have a stronger 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.

Irritant responses occur without sensitization. An irritant is any agent that is capable of producing cell damage and/or an inflammatory response 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. Allergic responses (*e.g*., allergic contact dermatitis) can be localized but may also have widespread skin involvement, particularly in patients with strong sensitization.

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 is capable of inducing 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*

- o *Frequency of occurrence and range of severity of reactions in healthy or susceptible populations*
- o *The result of experimental assays in animals or humans (considering dose-response factors), with human data taking precedence over animal data*
- o *Other data on potency or bioavailability of sensitizers*
- o *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*
- o *The threshold of human sensitivity*
- o *Epidemiological studies*
- o *Case histories*
- o *Occupational studies*
- o *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 significant sensitizer if the frequency of sensitization to that substance in the general population is greater than or equal to 1 percent. 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 percent or 95 percent of the general population is sufficient and/or appropriate.[84] For the determination of a threshold value, some of the panelists indicated that data exists for chemicals (*e.g*., isocyanates, colophony, plicatic acid) that could be used as benchmarks for estimating an appropriate frequency of occurrence in the general population. For protein allergens, some of the panelists suggested that 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*[85] 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:

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

[84] HESI Immunotoxicology Technical Committee, Respiratory Hypersensitivity Workshop, Washington, DC, June 2004.
[85] *Guides to the Evaluation of Permanent Impairment, 5th Edition, AMA Press, 2001*

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) and *in silico* data be added as additional considerations.[86]

CSPC Staff Discussion and 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.,* using 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.[87]

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 might be considered as "strong

[86] 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 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.

[87] 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.

sensitizers" due to widespread exposure to the general population if emphasis is placed on frequency of exposure. These examples place risk assessment considerations into the hazard identification step.

Rather than use the terms "quantitative or qualitative risk assessment", it may be more appropriate to use terms to define what is being sought from the listed factors, i.e., that quantitative or qualitative data derived from the remaining factors listed in this section that have the potential to provide sufficient information for determining the potency of a substance -- 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 "qualitative or quantitative assessment" should be removed from the supplemental definitions and that "qualitative and quantitative" be used to define the data for the listed factors.

During the discussion on ***frequency of occurrence***, the panelists suggested that a numerical ***threshold*** (i.e., cut-off) be provided. This threshold, tolerable level of sensitization/allergy prevalence, would function as a guide for indicating when frequency of occurrence is significant for identifying and labeling a substance as a "strong sensitizer".

The panelists provided a list of chemicals to serve as a template in deriving a frequency of occurrence limit; however the list was comprised predominantly of occupational sensitizers. Because the degree of sensitization in the workplace can be greater than that of the general population due to greater exposure (both in time, concentration and product utilization) to the sensitizing agent, CPSC staff believes that caution needs to be employed in applying 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, yet the prevalence for the general population is estimated to be below one percent.[88] However, sensitization in the workplace can serve as a harbinger for consumer sensitization as observed with the preservative MCI/MI[89] which was known as a workplace allergen when it first came into use. It has since risen to the top 30 of allergic contact dermatitis allergens for the general population of North America.

[88] 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.
[89] MCI/MI: methylchloroisothiasolinone/methylisothiasolinone; Pratt et al, Dermatitis 2004, 15(4): 176-183.

Data for the determining a sensitization frequency cut-off limit, a tolerable level of sensitization/allergy prevalence, 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 one percent of the general population worldwide. The Institute of Medicine indicated that twenty percent of the general population will develop an allergy-related illness (sinusitis, rhinitis, bronchitis, asthma)[90]. 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 sensitization frequency cut-off limit for a "strong sensitizer" at 1 percent may be either overly protective or insufficiently protective. CPSC staff believes identifying a substance as a "strong sensitizer" based on sensitization frequency cut-off rate value is best considered by a case-by-case weight-of-evidence criteria, if sufficient data are available.

During the discussion of 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 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 use 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 result 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".

[90] IOM (Institute of Medicine), 1993. *Indoor Allergens: Assessing and Controlling Adverse Health Effects.* Washington DC, National Academy Press.

Tables provide ranges of values that take into account age and gender and other factors

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)[91] provide approaches that CSPC staff could use as a basis for developing similar guidelines for interpreting the supplemental definitions. The CPSC staff draft proposed guidelines could use 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.[92] Body site, potential for exposure to

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

[92] 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 used 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

compromised skin, and delivery enhancement (beyond simple chemical penetrability characteristics – such as transdermal delivery, skin piercing, etc.) are relevant factors that could be considered as well.

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 ("well-conducted 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 sensitizing strength of a chemical, occupational data could exaggerate the estimation of the sensitizing strength of a chemical to the consumer scenario. If exposure and dose-response relationships are taken into account, worker sensitization prevalence could be used to estimate prevalence in the exposed general population. "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:

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

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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 C.F.R. §1500.135(d)(2)

The panelists recommended the inclusion of QSARs and *in silico* data 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. At a recent WHO/IPCS meeting on skin sensitization risk assessment[93], one conclusion was that QSARs and expert systems for identifying sensitizing capacity though not validated may be used as part of a weight-of-evidence approach.

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 (quantitative and qualitative) for a number of factors, following a weight-of-evidence approach. Frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility will be considered. The following factors (if available), ranked in descending order of importance, should be considered:
>
> - Well-conducted clinical and diagnostic studies
> - Epidemiological studies, with a preference for general population studies over occupational studies
> - Well-conducted animal studies[94]
> - Well-conducted *in vitro* test studies[30]
> - Cross-reactivity data
> - Case histories
>
> Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, specific human sensitization threshold values, 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.

[93] The International Programme on Chemical Safety (IPCS), General Conclusions and Recommendations of an IPCS International Workshop on Skin Sensitization in Chemical Risk Assessment, World Health Organization, 2007.

[94] Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration and, use of appropriate controls.

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".

CSPC Staff Discussion and 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 allergic response severity (NAEPP guidelines[95] and W-AZS system[96]) 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:
>
> - well-conducted clinical and diagnostic studies
> - epidemiological studies, with a preference for general population studies over occupational studies
> - well-conducted animal studies[97]
> - well-conducted *in vitro* test studies[33]
> - cross-reactivity data
> - case histories

[95] 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).

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

[97] Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration and, use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP) and good epidemiological practice (GEP).

Frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility 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 a 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, specific human sensitization threshold values, 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[98]) 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."

CSPC Staff Discussion and 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 percent 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.[99] 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[100]. 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.

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

[99] 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.

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

The term “non-sensitized” is the more appropriate term for what would be 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*)[101] 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 hypersensitivity 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 membranes, specifically highlighting ocular and oral systems.

CSPC Staff Discussion and Summary
The panelists recommended consideration of other organ systems, including mucosal membranes, 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

[101] 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).

evidence exists to clearly separate the sensitization characteristics (*e.g*., different mechanisms of sensitization) of the different target organs.

The CPSC staff draft proposed **revision to section** (v)[102] would read:

> *Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin, mucous membranes (*e.g*., ocular, oral) and other organ systems such as the respiratory tract and gastrointestinal tract, 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 used 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.*

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

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 (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 CSPC Staff Discussion and 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.

CSPC Staff Discussion and 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)[103] 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.[104] 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. At a recent WHO/IPCS workshop on skin sensitization risk assessment[105], it was concluded that the LLNA is the preferred test method for assessing the skin sensitization ability of chemicals in view of animal welfare considerations (the LLNA avoids potential pain and distress associated with positive results in the guinea pig tests). However, the expert group stated that there remains a need for guinea pig tests

[103] 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.

[104] Basketter et al, Contact Dermatitis 2005, 52: 39-43; Gerberick et al, American Journal of Contact Dermatitis 2001, 12(3): 156-161; Gerberick et al, Dermatitis 2005, 16(4): 157-202; Griem et al, Regulatory Toxicology and Pharmacology 2003, 38: 269-290; Kimber et al, Food and Chemical Toxicology 2003, 41: 1799-1809; Schneider et al, Regulatory Toxicology and Pharmacology 2004, 39: 245-255.

[105] The International Programme on Chemical Safety (IPCS), General Conclusions and Recommendations of an IPCS International Workshop on Skin Sensitization in Chemical Risk Assessment, World Health Organization, 2007.

particularly in testing of aqueous solutions, extracts, fabrics, mixtures and preparations. The expert group felt that: (1) any test of skin sensitizing capability that includes dose-response assessment can be used to assess potency, (2) currently the LLNA is the most appropriate assay for single chemical substances, as it is the only test for whose guidelines indicate to include dose-response assessment, (3) guinea pig data may also be used to categorize a chemical according to its skin sensitizing potency, (4) it is acknowledged that categorization of skin sensitizing potency is associated with a degree of uncertainty and, (5) neither the approach using the LLNA, nor the approach using guinea-pig data have been validated for the purpose of potency assessment.

WHO/IPCS workshop attendees made the following recommendations: (1) there is a need for a standardized system of classifying and determining limits according to potency, (2) that the use of the LLNA for potency categorization of induction of skin sensitization needs to be validated, (3) that further studies should be carried out regarding potency ranking of chemicals according their potency to elicit allergic responses in individuals diagnosed with contact allergy and, (4) that the LLNA needs to be further developed with a view to testing aqueous solutions, preparations and complex mixtures.

Historically, the GPMT and the BA are the primary animal assays that have been used to determine the sensitizing ability of a chemical focusing on whether or not a substance is a sensitizer. These assays have been modified to determine potency. Experimental animal data and human data can be used for determining sensitizing strength. One approach by a panel of German experts ranked 244 substances into three categories based on potency.[106] 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). Therefore in the Schlede et al approach, Category A, significant allergen, could be analogous to the subset of strong sensitizers as defined in the FHSA.

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.

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

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 could 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 at this time 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.

Since the initial preparation and review of the technical report, ICCVAM accepted a nomination from CPSC to evaluate the LLNA as a stand-alone assay for potency determinations for classification purposes, as well as to assess the usefulness of the LLNA for assessing the skin sensitization potential of mixtures, aqueous solutions, and metals (January 2007). ICCVAM was also requested to address the susceptibility of the assay to vehicle effects.[107] The ICCVAM analysis is based on a comprehensive review of LLNA, guinea pig and human data derived from a database of over 500 substances, 170 of which have comparative LLNA, guinea pig and/or human data. For each substance with comparative LLNA, guinea pig or human data, potency was evaluated by comparing the LLNA EC3 concentration against the threshold concentration inducing the human response; for guinea pig data it was the percentage of responding animals and the associated induction concentration. ICCVAM convened the LLNA Peer Review Panel at CPSC in March 2008 to address the charges as outlined by ICCVAM. The panel report should be available mid-year, with final recommendations available in late 2008. CPSC staff will consider these recommendations and revise its recommendations as needed.

[107] Many factors impact skin sensitization, one of which is the ability of the substance to traverse the stratum corneum and reach the epidermis. The vehicle in which the chemical is suspended/solubilized can alter the skin penetration of the test substance. Published literature in which the LLNA has been used for potency determinations, has demonstrated variability in classifications into potency categories for the same chemical, the difference due to different vehicles (solvents) used.

C. Question #3

Immunotoxicology[108] 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 used 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 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, described in Appendix D) has been shown to be a good tool for identifying protein allergens, however, along with the new approach of "cytokine profiling" (described in Appendix D), 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 (described in Appendix D) diminishes its applicability for use in classification and identification of sensitizers. This assay is also limited to assessing just IgE-mediated allergens[109].

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[108] 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).

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

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

CSPC Staff Discussion and Summary

Although progress has been made with both animal models and alternative methods, there still is no validated approach to assess respiratory hypersensitivity potential. As recommended in the WHO/IPCS 2007 report and by Holsapple et al,[110] there is a continued need for the development of methods and criteria to assess the potential of proteins, chemicals and drugs in inducing respiratory hypersensitivity.

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, using 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.

CPSC staff will consider the ICCVAM recommendations on the LLNA when they become available and will revise its recommendations as needed.

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 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

[110] Holsapple et al, Toxicological Sciences 2006, 91(1): 4-13.

occur early in life through contact with consumer products and medical materials.[111] 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 Childhood Asthma[112]. These longitudinal studies followed large randomly

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

[112] 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.

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.[113] Large cohort studies on aeroallergens were provided by some of the panelists as evidence of the increased susceptibility of children.[114] In one study, 18 percent of the infants (mean age was 13.7

[113] Atopy is a genetic predisposition to allergy and for producing IgE antibodies. Reports in published literature indicate that at least 20 percent to 40 percent of the general population is atopic.
[114] 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;

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 prenatal 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[115] was of greater concern to the panelists. The report demonstrated that 52 percent 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 panel member stated that he was not aware of differences in skin properties between neonates, infants and adults). The panelists who

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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.

[115] von Mutius E et al., Thorax 2001, 56(11):835-838.

believe there is no increased sensitivity in children with regards to skin sensitizing substances, stated that reactivity to 2,4-dinitrochlorobenzene (DNCB)[116] has been shown to be low in infants, and allergic dermatitis to poison ivy-oleorisin is rarely seen in early life. In contrast, an experimental study on DNCB sensitization in infants showed low reactivity just after birth; however, susceptibility increased to adult levels over the period of the first 9 months of life, reflective of developing immunocompetence in neonates.[117] 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.

CSPC Staff Discussion and 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 percent over the past two decades, while the rate among children under the age of 5 has increased over 160 percent.[118] Data that exist comparing children to adults is the NHANES III study provided by a

[116] DNCB is the chemical most often used in studying the mechanism of allergic contact hypersensitivity.
[117] Cassimos et al, J. Clin. Lab. Immunol 1980, 3(2):111-113.
[118] 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.

panelist, this data demonstrates a higher prevalence of atopy in young versus adult populations in the United States.

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). A recent murine study demonstrated an increase in risk of asthma in the offspring of mothers with allergic contact dermatitis.[119] At 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 shown definitively. 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[120]. 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, ethylenediamine, thimerosal, merbromlin (mercurochrome), balsam of Peru, rubber chemicals in shoes and poison ivy[121]. 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.

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[119] Lim et al, Respiratory Research 2007, 8: 56-60.
[120] 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.
[121] Fisher's Contact Dermatitis, 2001, 5th edition, Rietschel RL and Fowler J, eds. Lippincott, Williams and Wilkins, New York.

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 increased more than 300 percent since the 1960s.[122] 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.

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

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

CSPC Staff Discussion and 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.[123] 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.[124] 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

[123] Some human sensitization testing (*e.g.*, Human Repeat Insult Patch Test [HRIPT]) is often done using products or product formulations. In addition, the preferred vehicle for the LLNA is a mixture of acetone and olive oil.
[124] Lea LJ et al., Am J Contact Dermat 1999 Dec, 10(4):213-8.

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 includes testing the entire formulation as well as the drug vehicle for sensitizing potential.[125]

IV. Overall CSPC 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 C.F.R. §1500.3(b)(9)) and supplemented in §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.

<u>Question 1, Supplemental Definition of Sensitizer</u>
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

[125] 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.

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 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, well-conducted).
- 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 use 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 mucosal membranes, 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 is capable of inducing 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.

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

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 hypersensitivity 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:

- well-conducted clinical and diagnostic studies
- epidemiological studies, with a preference for general population studies over occupational studies
- well-conducted animal studies[126]
- well-conducted *in vitro* test studies[55]
- 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 exposed subpopulations having average or high susceptibility 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

[126] Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration and, use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP) and good epidemiological practice (GEP).

A clinically important reaction would be considered one with a 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, specific human sensitization threshold values, 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, mucous membranes (*e.g*., ocular, oral), and other organ systems such as the respiratory tract and gastrointestinal tract, 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[127], 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.[128] 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

[127]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.
[128]15 U.S.C. §1261(f)(1)(A)

other article is entrusted, then the product is by definition a “banned hazardous substance” unless specifically exempted by regulation.[129]

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.

[129] 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[130] (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 antibodies (*e.g.*, IgM, IgG, or IgE). 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 approximately 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 formed during sensitization (also known as the induction phase), released into the systemic circulation and bound to mast cells and basophils. 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 and basophils to release a variety of substances (*e.g.*, histamine, heparin, prostaglandins, leukotrienes), including cytokines. These substances have acute symptom generation capacity (*e.g.*, histamine causes airway smooth muscle contraction, vasodilation, plasma extravasation, sensory nerve stimulation and neural reflex generation). Presentation of allergen to T-helper 2 (Th2) type cells causes this subset of T lymphocytes to produce a panel of cytokines that are key to allergic disease, including 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 tract may respond after dermal exposure to the causative agents. At this time, skin sensitization after inhalation exposure has not been clearly demonstrated.

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

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. A key metric for skin sensitization is the dose per unit area of exposed skin. 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 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[131]

Respiratory system

The American Medical Association (AMA) used 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,[132] 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.

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

[132] 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.

- forced expiratory volume in the first second (FEV_1). FEV_1 assesses air flow dynamics within the bronchi
- 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) because 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 percent to 100 percent 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 percent 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 percent to 54 percent:

- Class 1: 0−9 percent 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 percent impairment of the whole person
    - signs/symptoms present or intermittently present
    - limited performance of some ADL
    - intermittent to constant treatment
- Class 3: 25−54 percent impairment of the whole person
    - signs/symptoms present or intermittently present
    - limited performance of many ADL
    - intermittent to constant treatment
- Class 4: 55−84 percent 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 percent 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 disabling. In examples provided in the handbooks, one case of severe dermatitis was listed with an impairment classification of 9 percent, 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 percent; 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 hyper-responsiveness (AHR) is a characteristic feature of the lungs of asthmatic individuals, though it can also be found in individuals with nonallergic conditions of airflow obstruction (*e.g.*, chronic obstructive pulmonary disease [COPD]). Inhaled stimuli, such as environmental allergens, can increase airway inflammation and enhance AHR. Changes in AHR can be smaller in healthy subjects than those measured in asthmatic patients with persistent AHR; they are similar to the changes occurring in asthmatic patients with worsening asthma control. Therefore measurements of AHR 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)[133]
- pulmonary function tests (*e.g.*, spirometry, peak flow measurements, plethysmography, diffusing-capacity, exercise studies, rhinomanometry).

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.[134] These guidelines propose that asthma

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

[134] 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, [135] 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 PEF measurements)[136], 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.

[135] 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

[136] FEV (forced expiratory volume) and PEF (peak expiratory flow). Described in Appendices A and G.

	Symptoms	Nighttime Symptoms	Lung function	Medications[137]	**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)

[137] 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 contact dermatitis is characterized by erythematous macules (discolored spots) and papules (circumscribed solid elevated areas on the skin with no visible fluid which usually precede vesicle and pustule formation), edema, fluid-filled vesicles or bullae (blisters), 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.[138]

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.[139] Three systems were considered to assess severity: W-AZS, Emerson et al[140] and IGADA (Investigator Global Atopic Dermatitis Assessment)[141]. These systems use some or all of the above mentioned criteria. CSPC staff proposes utilizing a simplified version of the W-AZS severity scoring system[142] 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). 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.

[138] Charman CR et al., Arch Dermatol 2005 Sep; 141:1146-51.
[139] Williams HC, NEJM 2005 June; 352(22):2314-24.
[140] 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 used 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.
[141] 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.
[142] Silny W et al., Acta Dermatov Croat 2005; 3(4):219-24.

Severity Index Score = I + II[143]

- **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 — **D: Severity signs of inflammation**

Body areas:			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

[143] 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[144] 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 use 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 percent 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 percent 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

[144] Defined in Appendix G

sensitizer. Published 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 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 assessing the induction of IgE responses 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[145] 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 stand-alone assay for potency determination, and the sensitivity of the assay needs improvement. At this time cytokine profiling per se is a procedure measuring additional read-on parameters that may be added to a series of sensitization tests such as the LLNA.

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

[145] Defined in Appendices A and G

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 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 C.F.R. §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 exposed 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 is capable of inducing 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 hypersensitivity 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:

- Well-conducted clinical and diagnostic studies
- Epidemiological studies, with a preference for general population studies over occupational studies
- Well-conducted animal studies[146]
- Well-conducted *in vitro* test studies[75]
- 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 exposed subpopulations having average or high susceptibility 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:

[146] Criteria for a "well-conducted" study would include validated outcomes, relevant dosing and route of administration and, use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP) and good epidemiological practice (GEP).

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

A clinically important reaction would be considered one with a 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, specific human sensitization threshold values, 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 mucosal membranes (*e.g*., ocular, oral), and other organ systems such as the respiratory tract and gastrointestinal tract, 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[147], 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.[148] 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

[147]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.
[148]15 U.S.C. §1261(f)(1)(A)

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.[149]

[149]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 used for the determination of sensitizing ability (see Appendix D)
Bullae – large blisters filled with fluid, size is larger than 1cm
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
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; subtypes include irritant contact dermatitis, allergic contact dermatitis
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 used 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 – syn. Antibody; a high molecular weight protein produced by B-lymphocytes during an immune response,
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 cellular response to local cell damage involving tissue infiltration of cells of the immune system caused by release of signalling molecules (cytokines) that is not mediated by specific immune recognition via T-cell receptor or immunoglobulins
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 used 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 circumscribed solid elevations on the skin with no visible fluid
PEF – 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, can be rare in allergic contact dermatitis
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 three 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, also called wheals or hives; the lesions are plateau-like edematous elevations of the skin which can change size, shape and location quickly and usually occur as an allergic reaction.
Vesicle – a small elevation on the skin containing serous fluid, blisters less than 1cm in size