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,[1] 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.[2] 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.[3] 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."[4] 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.[5]

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[1]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.

[2]16 C.F.R. §1500.3(b)(4)(i)(A).

[3] 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."

[4] 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*.

[5]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.[6]

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.[7] 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.[8] 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.

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[6] Updated strong sensitizer supplemental definition 16 C.F.R. §1500.3(c)(5).
[7] The production of IgE antibodies is typical of Type I hypersensitivity reactions (*e.g.*, rhinitis, urticaria).
[8] 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."[9] 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.[10]

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;

[9] 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.
[10] Updated strong sensitizer supplemental definition 16 C.F.R. §1500.3(c)(5).

(E) cross-reactivity data;
(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.[11] 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

[11] 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.

sensitizers. Because recognized and validated test methods currently are not available, identification of respiratory sensitizers is based on the induction of 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).[12] 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.[13] 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

[12] 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).
[13] The LLNA provides a yes/no answer about whether a substance is a sensitizer.

potential of most types of substances. 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. 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*[14] 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.[15] 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

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

[15] 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.

contribute to risk in all populations studied.[16] 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 past 2 decades, while the rate among children under the age of 5 has increased more than 160 percent, and it continues to rise.[17] 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.[18] 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.[19] 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.

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[16] 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.

[17] 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.*

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

[19] 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.

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 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*[20]

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

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

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 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.[21] However, sensitization in the workplace can serve as a harbinger for consumer sensitization, as observed with the preservative MCI/MI,[22] 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).[23] 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.

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[21] 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.
[22] MCI/MI: methylchloroisothiasolinone/methylisothiasolinone; Pratt et al, Dermatitis 2004, 15(4): 176−183.
[23] IOM (Institute of Medicine), 1993. *Indoor Allergens: Assessing and Controlling Adverse Health Effects.* Washington DC, National Academy Press.

1. Determining the Severity of Respiratory and Skin Sensitization Responses

a. Respiratory

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 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.[24] 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,[25] these guidelines are in line with the American Medical Association's (AMA) respiratory impairment guidelines and tests recommended by the IOM.

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[24] 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.

[25] 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

Tests of pulmonary function (particularly FEV_1 and PEF measurements),[26] 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.

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.

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

	Symptoms	Nighttime Symptoms	Lung Function	Medications[27]
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)

[27] 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.[28]

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.[29] Three systems were considered to assess severity: W-AZS, Emerson et al[30] and IGADA (Investigator Global Atopic Dermatitis Assessment).[31] 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[32] 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."

[28] Charman CR et al., Arch Dermatol 2005 Sep; 141:1146-51.
[29] Williams HC, NEJM 2005 June; 352(22):2314-24.
[30] 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.
[31] 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.
[32] Silny W et al., Acta Dermatov Croat 2005; 3(4):219-24.

Severity Index Score = I + II[33]

- **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

[33] 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.[34]

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.

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