

U.S. Consumer Product Safety Commission Strong Sensitizer Supplemental Definition



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These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

U.S. Consumer Product Safety Commission

- Independent, Federal regulatory agency; est. 1973
- Mission is to reduce unreasonable risks of injury from consumer products
- Jurisdiction includes thousands of different types of products sold to consumers for personal use in or around the household or school and in recreation (does not include cars, airplanes, foods, medical devices, tobacco, or pesticides)

Regulatory Authorities

- Consumer Product Safety Act (CPSA),
15 U.S.C. § 2051-2084
- Federal Hazardous Substances Act (FHSA),
15 U.S.C. § 1261-1278
- Consumer Product Safety Improvement Act of
2008 (CPSIA)
- Labeling of Hazardous Art Materials Act
(LHAMA)
- Poison Prevention Packaging Act (PPPA)

Consumer Product Safety Improvement Act of 2008

- Signed into law August 14, 2008 (Public Law 110-314)
- Expands CPSC's authority for a wide range of products
- Establishes product standards and other safety requirements for children's products and reauthorizes and modernizes the CPSC

CPSIA Provisions

- **Lead Paint & Lead in Children's Products:** set new limits on lead content for paint and other materials and components
- **Phthalates:** prohibited sale of certain children's products containing 1 or more of DEHP, DBP, or BBP; temporarily banned other phthalates pending further study
- **Mandatory Toy Standards:** ASTM F-963
- **Durable Nursery Products:** new mandatory standards; registration card requirements

CPSIA Provisions (continued)

- **Mandatory Certification:** manufacturers must certify compliance before importing and distributing; certification of children's products must be based on testing by accredited third party laboratory
- **Tracking Labels**
- **Product safety database:** public searchable web-based database
- **Sale of recalled products is prohibited**
- **Penalties:** civil penalties increased
- **Whistleblower Protections**

Children's Product Definition

- A children's product is defined under the CPSIA as a consumer product designed or intended primarily for children 12 years of age or younger
- CPSC will consider manufacturer's statement about intended use, packaging, display, promotion or advertising, and staff's Age Determination Guidelines

Federal Hazardous Substances Act (FHSA)

- Authorizes action when a product is or contains a “hazardous substance,” 15 U.S.C. § 1261(f)
 - Covers substances that are toxic, corrosive, an irritant, strong sensitizer, flammable or combustible, or generates pressure through decomposition, heat or other means; considers exposure; requires case-by-case hazard assessment
- Toy or other article intended for children and containing a hazardous substance is a banned hazardous substance, 15 U.S.C. § 1261(q)(1)
- Product not specifically intended for children may require precautionary labeling, 15 U.S.C. § 1261(p)

Sources of Information

- Investigations
- National Electronic Injury Surveillance System (NEISS); other databases
- CPSC SaferProducts.Gov, CPSC Hotline complaints/inquiries
- Written and oral communications
- Federal, state and local governments

Possible Hazard Reduction Actions

- Development of voluntary and mandatory standards
- Product recall, replacement, refund, redesign
 - www.cpsc.gov, www.recalls.gov
- Consumer information:
 - Publications; press & video releases; social media
 - Neighborhood Safety Network Program (Boys & Girls Clubs, Indian Health Services, HUD, Meals on Wheels, fire departments)

Strong Sensitizer Definition

- Statutory definition appears in section 2(k) of the FHSA 15 U.S.C. § 1261(k):

The term ‘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 a significant potential for causing hypersensitivity.

Strong Sensitizer Supplemental Definition of 1986

- *(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*

Strong Sensitizer Supplemental Definition of 1986 (continued)

- *(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 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.*

Strong Sensitizer Supplemental Definition of 2014

(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.

Strong Sensitizer Supplemental Definition of 2014 (continued)

(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. The determination may be based on documented medical evidence of hypersensitivity reactions upon subsequent exposure to the same substance obtained from epidemiological surveys or case histories; controlled *in vivo* or *in vitro* experimental studies; susceptibility profiles (e.g., genetics, age, gender, atopic status) in non-sensitized or allergic subjects; and chemical or functional properties of the substance.

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; and
- (F) case histories.

Strong Sensitizer Supplemental Definition of 2014 (continued)

(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. Bioavailability 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.

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).

Strong Sensitizer Supplemental Definition of 2014 (continued)

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 physiological effects, such as discomfort and distress;
 - (B) substantial hardship;
 - (C) functional or structural impairment;
 - (D) persistent morbidity;
- or in rare cases, mortality.

(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.

Strong Sensitizers

- 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.

Strong Sensitizer Guidance Document, 2013

- For a product containing a strong sensitizer 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.
- 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 it is not based solely on the presence of a strong sensitizer in a product.

Strong Sensitizer Guidance Document (continued)

- The designation of a substance as a “strong sensitizer” is a Commission-made determination.
- 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.
- 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.”

Strong Sensitizer Guidance Document (continued)

- 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. 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.

Strong Sensitizer Guidance Document (continued)

- 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.

Strong Sensitizer Guidance Document (continued)

- 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. Epidemiological studies (general population studies) are preferred over occupational studies.
 - Existing high-quality data
 - Flexibility for use of new validated technologies
 - Susceptible Populations
 - Frequency of occurrence
 - Case-by-case
 - Example: wide exposure with mild symptoms

Guidance Document – Respiratory Sensitization

- Severity of Reaction: a clinically-important reaction
- Respiratory Sensitization
 - 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).
 - Guidelines for the Diagnosis and Management of Asthma
 - 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.

Guidance Document – Respiratory Sensitization (continued)

Moderate Persistent	Symptoms	Nighttime Symptoms	Lung Function	Medications
	Daily; daily use of short-acting beta2 agonists, exacerbations occur \geq 1x/week; can last several days	> 1x/week	FEV1 or PEF >60% and <80% predicted; PEF variability >30%	Long-term: low-to-medium dose of corticosteroids & long-acting inhaled beta2 agonists or with leukotriene modifier or theophylline
Severe Persistent	Symptoms	Nighttime Symptoms	Lung Function	Medications
	Continual; limited physical activity; frequent exacerbations	Frequent	FEV1 or PEF \leq 60% predicted; PEF variability >30%	Long-term: high dose corticosteroids & long-acting inhaled beta2 agonists & (if needed) corticosteroid tablets

Guidance Document – Skin Sensitization

■ Skin Sensitization

- Lack of consensus and a lack of standardization in disease severity scoring for ACD. More than 50 different clinical scoring systems have been identified in the 93 randomized controlled clinical trials published between 1994 and 2001.
- 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

Guidance Document – Skin Sensitization (continued)

- Three systems were considered to assess severity: W-AZS, Emerson et al, and IGADA (Investigator Global Atopic Dermatitis Assessment). These systems use some or all of the above-mentioned criteria.
- Simplified version of the W-AZS severity scoring system 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.”
- Severity Index Score = I + II
 - Section I: (A) based on extent, frequency & severity of pruritus, and (B) loss of sleep
 - Section II: (C) location & extent of lesions, and (D) severity of skin inflammation

Questions?

Thank you!

<http://www.cpsc.gov/global/regulations-laws-and-standards/regulated-products-rules/strongsensitizerguidance.pdf>.

Contacts

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