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

BALLOT VOTE SHEET

This document has been electronically approved and signed.

Date: January 29, 2014

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Stephanie Tsacoumis, General Counsel
Elliot F. Kaye, Executive Director

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

SUBJECT : Final Rule: Revision of Strong Sensitizer Supplemental Definition

BALLOT VOTE Due: February 4, 2014

Attached is the draft *Federal Register* notice for the final rule revising 16 C.F.R. part 1500, to amend the CPSC's supplemental definition of "strong sensitizer."

Please indicate your vote on the following options on the final rule:

I. Approve publication of the attached document in the *Federal Register*, as drafted.

_____ _____
(Signature) (Date)

II. Approve publication of the attached document 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)

Attachment: Draft *Federal Register* notice of Final Rule: Revisions to Supplemental Definition of “Strong Sensitizer”

Billing Code 6355-01-P

CONSUMER PRODUCT SAFETY COMMISSION

CPSC Docket No. CPSC-2013-0010

16 CFR Part 1500

Hazardous Substances and Articles; Administration and Enforcement Regulations:

Final Rule; Revisions to Supplemental Definition of "Strong Sensitizer"

AGENCY: Consumer Product Safety Commission.

ACTION: Final Rule.

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

DATES: The rule will become effective on [INSERT DATE THAT IS 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Carol Afflerbach, Compliance Officer, Office of Compliance and Field Operations, U.S. Consumer Product Safety Commission, 4330 East-West Highway, Bethesda, MD 20814; e-mail: cafflerbach@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

containing substances that are toxic, corrosive, an irritant, flammable or combustible, generate pressure through decomposition, heat or other means, or are 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 U.S. 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" by explaining that a " 'strong allergic sensitizer' is a substance that produces an allergenic sensitization in a substantial number of persons that come into contact with it" and specifying that "[a]n allergic sensitization develops by means of an 'antibody mechanism' in contradistinction to a primary irritant reaction which does not arise because of the participation of an 'antibody mechanism.'" 26 FR 7333, 7334. The regulation (the 1961 supplemental definition) listed five substances that the FDA had determined met the statutory definition for "strong sensitizer": (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. *Id.* at

7335. Neither the FDA nor the CPSC added any strong sensitizers to this list in the 1961 supplemental definition.

In 1973, Congress transferred the responsibility for the administration of the FHSA to the Commission. On May 30, 1984, the Commission revoked the 1961supplemental definition because the 1961 supplemental definition did not account for more recent scientific theories and was narrower than the statutory definition. 49 FR 22464.

On August 14, 1986, the Commission issued a rule supplementing the statutory definition of "strong sensitizer" (1986 supplemental definition). 51 FR 29094. The 1986 supplemental definition clarified how the statutory definition should be interpreted and explained the factors the Commission would consider in determining whether a substance is a strong sensitizer. The 1986 supplemental definition stated 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 1986 supplemental definition also clarified 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 a reaction after reapplication of the same substance—are included in the class of substances that can be determined to be strong sensitizers. The 1986 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.

In 2005, recognizing that the science on sensitization had changed since promulgation of the 1986 supplemental definition, 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." Based on the panel's input, CPSC staff developed a draft technical report on proposed revisions to the supplemental definition. In 2007, the draft technical report underwent federal agency and external scientific peer review. In 2008, CPSC staff revised the draft technical report based on the input received from federal agency and external scientific peer reviewers. Subsequently, CPSC staff drafted a revision of the "strong sensitizer" supplemental definition, based on the peer reviewed technical report.

The Commission approved publication of a notice of proposed rulemaking (NPR) to revise the supplemental definition of "strong sensitizer" (proposed definition or proposed rule). 78 FR 15660 (March 12, 2013). The proposed definition of "strong sensitizer" eliminates redundancy, removes certain subjective factors, incorporates new and anticipated technology, ranks the criteria for classification of strong sensitizers in the order of importance, defines criteria for "severity of reaction," and provides for the use of a weight-of-evidence approach to determine whether a substance is a strong sensitizer.

In addition, the Commission approved publication of a notice of availability for a document prepared by CPSC staff titled, "Strong Sensitizer Guidance." 78 FR 15710 (March 12, 2013). This guidance document was intended to clarify each component of the revised "strong sensitizer" definition and assist manufacturers in understanding how CPSC staff would assess whether a substance or product containing that substance should

be considered a strong sensitizer and how the Commission would make such a determination.

B. Response to Comments on the Proposed Rule

We received five comments on the NPR. The following individuals or entities submitted comments: a consulting toxicologist; the International Fragrance Association of North America; the People for the Ethical Treatment of Animals (PETA); the International Science Consortium and the Physicians Committee for Responsible Medicine; the American Chemistry Council; and the Diisocyanates Panel of the American Chemistry Council.

Several commenters expressed general support for the proposed rule and made statements supporting specific aspects of the rule. For example, several commenters supported deleting the reference to sensitizers that occasionally induce an allergic response on first exposure so that substances that merely cause irritation upon initial exposure will not be considered strong sensitizers. Similarly, a commenter agreed with the proposal's emphasis that sensitization is an immunologically mediated, multi-stage process that occurs over a period of time. Several commenters raised issues that resulted in minor organizational and terminology changes to the proposed rule. All of the comments can be viewed at: www.regulations.gov, by searching under the docket number of the rulemaking, CPSC-2013-0010. Following is a summary of, and responses to, the comments.

Harmonization with International Criteria

Comment: Two commenters recommended that the CPSC take action to align the agency's chemical classification regulations and practices with internationally

harmonized criteria, encouraging the Commission to implement the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). One of the commenters argued that harmonization of chemical classification and labeling will promote regulatory efficiency and facilitate trade without lowering the level of health and environmental protection afforded by current U.S. laws and regulations. One of the commenters recommended that the Commission use the GHS cut-off value criteria for determining whether a substance is a sensitizer, unless there has been sensitization testing on the substance or product containing the substance.

Response: The GHS is a system for standardizing and harmonizing the classification and labeling of chemicals, but the GHS is not a regulation or a standard. The intent of the GHS is 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 establishes agreed-upon hazard classification and communication criteria with explanatory information on how to apply the system. Implementation of the GHS by the Commission would be broad-reaching, with potential impact beyond the FHSA, possibly involving the revision of existing CPSC statutes and regulations. The request that the Commission implement the GHS, therefore, goes well beyond the limited scope of this rulemaking proceeding.

Description of Strong Sensitizer Determination Process

Comment: Two commenters requested a description of the administrative process that would be used to make a determination that a substance or product containing a substance is a strong sensitizer so that stakeholders will be aware of opportunities for participation in the process.

Response: Under the FHSA, the Commission must first designate a substance a "strong sensitizer" for the substance to be considered a "strong sensitizer." (15 U.S.C 1261(k)). Such a designation would occur in a separate proceeding that is outside the scope of this action. The current action relates only to the regulatory definition of a "strong sensitizer," not to the designation of a particular substance as a strong sensitizer.

Labeling Requirement for Strong Sensitizers

Comment: One commenter requested that the Commission set forth the circumstances under which a substance or product containing a substance that has been designated a strong sensitizer would not require labeling under Section 2(p) of the FHSA (15 USC 1261(p).

Response: A substance that is a strong sensitizer or a product containing a strong sensitizer would not require labeling, unless the substance met the FHSA definition of "hazardous substance." A "hazardous substance" is one that is a strong sensitizer (or has another of the specified "hazardous substance" characteristics) and "may cause 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). Thus, manufacturers of products containing a strong sensitizer would have to determine whether the concentrations and availability of the substance in their products could cause substantial injury or illness as a result of reasonably foreseeable handling or use. Labeling under section 2(p) of the FHSA would only be required if the product containing a strong sensitizer would cause substantial injury or illness as a result of reasonably foreseeable handling or use.

The Commission would also have the option of issuing a rule under Section 3(a) of the FHSA to designate a strong sensitizer as a hazardous substance to reduce uncertainty about which products would be considered a hazardous substance. *Id.* § 1262(a)(1). A hazardous substance that is not labeled properly with appropriate cautionary statements in accordance with section 2(p) of the FHSA is considered a "misbranded hazardous substance." *Id.* § 1261(p). Introducing, delivering for introduction, or receiving in interstate commerce a misbranded hazardous substance is a prohibited act. *Id.* § 1263(a) and (c).

Effect of Rule on Regulation of Products and Risk Management Actions

Comment: One commenter asserted that replacing the 1986 supplemental definition with the proposed definition could have far-reaching effects on the regulation of products at a broader level and stated that classifying substances as strong sensitizers may prompt risk management actions by the CPSC or other regulatory bodies. The commenter encouraged the CPSC to see that classification determinations fully reflect a science- and risk-based approach that considers the degree of hazard and extent of exposure potential.

Response: The Commission does not believe that replacing the 1986 supplemental definition with the final rule definition will have "far-reaching effects." The rule does not designate any particular substance as a strong sensitizer, but the rule revises the regulatory definition of "strong sensitizer." A separate proceeding involving a specific substance would be required before the agency could declare a substance to be a strong sensitizer. This rule simply provides guidance about the information and data that CPSC would consider and the relative importance of the information in making a strong sensitizer determination.

Moreover, the determination that a substance is a strong sensitizer does not, by itself, require any action by a manufacturer. Under the FHSA, labeling or other regulatory action implicating risk management factors is required only when a substance meets the definition of "hazardous substance." (15 U.S.C. 1261(f)). A substance that the Commission designates as a strong sensitizer could be a "hazardous substance" under the FHSA, "if such substance or mixture of substances may cause 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." Therefore, by definition, the FHSA considers exposure and requires a case-by-case hazard assessment. The final rule definition reflects both a science- and risk-based approach so that the decision for classification is not based solely on a product's ingredients.

Separate Treatment of Type I and Type IV Allergies in Sensitizer Definition

Comment: One commenter recommended that Type I and Type IV allergies be addressed separately in the final rule definition because these types of allergies have different potential for causing illness, discomfort, and chronic morbidity; and consideration of different types of data would be necessary to evaluate the potential of substances that trigger these two different types of reactions to cause substantial illness.

Response: A Type I allergy or immediate hypersensitivity is an allergic reaction provoked by reexposure to a specific type of allergen due to the production of specific antibodies. A Type IV allergy or delayed hypersensitivity is an allergic reaction that typically arises 1 to 3 days after exposure to an allergen and is not an antibody-mediated response. We agree that evaluating whether a substance is a strong sensitizer will depend

on the substance and the allergic response the substance induces. However, we believe that the final rule definition would be significantly and unnecessarily more complex if these two types of allergies were separated into different categories.

The criteria contained in the supplemental definition allow for flexibility in assessing all types of allergic reactions to sensitizers. In addition, the final rule definition includes the various potential routes of exposure for sensitizers, as well as anatomic sites of an allergic response. The outcome of exposure, whether a dermal or respiratory response, likely will require the analysis of different data for evaluation. Evaluating whether a substance is a strong sensitizer requires a case-by-case inquiry, based on high-quality relevant data. The Strong Sensitizer Guidance document explains the approach CPSC staff would take in evaluating the potential causal link between exposure to strong sensitizers and these two types of hypersensitivity. We believe that the final rule definition provides the flexibility for assessing these two types of allergic reactions to sensitizers without the need for specifically differentiating them.

Acceptance of Data from Certain QSAR Models

Comment: One commenter requested that the Commission revise the proposed definition to provide for the acceptance of data from Quantitative Structure-Activity Relationship (QSAR) models (mathematical models that relate a quantitative measure of chemical structure to biological activity) that the Organisation for Economic Co-operation and Development (OECD) has evaluated and approved for specific applicability domains.

Response: The final rule definition specifically states that in determining whether a substance has a significant potential for causing hypersensitivity, chemical or functional properties of the substance of interest, in addition to QSAR data, can be considered. The

panel of experts and external peer reviewers determined that QSAR data are not sufficient as stand-alone analyses for determining potency of a sensitizer but that QSAR analysis could be used in a weight-of-evidence approach.

The OECD Council Act relating to the Mutual Acceptance of Data (MAD), which was agreed to by all OECD member countries, established that safety data developed in one member country will be accepted for use by the relevant registration authorities in assessing the chemical or product in another OECD country (*i.e.*, the data do not have to be generated a second time for the purposes of safety assessment), under the assurance that the data were developed in compliance with the Principles of Good Laboratory Practice. Therefore, if a manufacturer submitted QSAR data to the Commission when the Commission was determining whether a substance is a strong sensitizer, the Commission would take the QSAR data into consideration. However, this QSAR data would not take precedence over high-quality human and animal data. The Commission believes that modifying the proposed definition in response to this comment is not warranted.

Ordering of Factors to be Considered in Determining Whether a Substance is a Strong Sensitizer

Comment: One commenter suggested revising the order of the factors that would be taken into consideration to determine whether a substance is a "strong" sensitizer and including a reference in that paragraph to unranked data that appears elsewhere in the proposed definition. The commenter requests: (1) shifting the order of factors as they appear in the paragraph listing the factors to be considered in determining whether a sensitizer is "strong" – for example moving "well-conducted animal studies" to the end of the list; (2) moving two of the unranked factors listed in the proposed supplemental

definition (quantitative structure-activity relationship information and bioavailability data) into the list of ranked factors as the third and fourth priority position; and (3) separating existing versus new *in vitro* and *in vivo* studies into different factor categories.

Response: CPSC based the order of ranked data criteria in the proposed definition on extensive input from the international panel of scientific experts from academia, industry, and the federal government. We concurred with the panelists' suggestion to rank and list the qualifying factors in order of importance in the final rule definition, instead of "any or all," which is how the factors appear in the 1986 supplemental definition.

The Commission believes that the ranked list of criteria for determining whether a substance or product containing a substance is a "strong" sensitizer should remain as stated in the proposed definition but that the reference to unranked factors, such as quantitative structure-activity relationship information, *in silico* data and bioavailability data, should be moved to the end of the list of ranked factors so that the order is more logical. The list of criteria reflects Commission policy that human data take precedence over animal data and takes into consideration the value and relevance that the particular data would provide in making a determination of sensitizing strength, and therefore, the potential to cause hypersensitivity. The criteria list is consistent with the CPSC Animal Testing Policy, the FHSA Chronic Hazard Guidelines, and Commission policy that strongly encourage the use of scientifically validated alternatives to animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results.

Consistency of Order of Factors Listed Throughout the Rule

Comment: One commenter pointed out that the factors to be considered in determining whether a substance has a "significant potential for causing hypersensitivity" were not listed in the same order when listed as factors to be considered in determining whether a substance is a "strong" sensitizer. The commenter requested that the Commission be consistent when listing the types of data in these two paragraphs.

Response: We agree that the order of factors should be consistent in these paragraphs. Therefore, we have modified the proposed definition by: (1) moving "chemical or functional properties of the substance" to the end of the last sentence in the first paragraph of section (ii); and (2) in the same sentence reversing the positions of *in vitro* and *in vivo*.

Use of Existing Animal Testing Data

Comment: One commenter recommended that we specify that existing animal testing data be submitted to the CPSC for consideration in making a strong sensitizer determination before additional animal testing data is generated.

Response: As stated in the CPSC Animal Testing Policy, codified at 16 CFR 1500.232, neither the FHSA, nor the regulations issued under the FHSA, require animal testing to determine whether a hazard exists. The Commission's regulations under the FHSA concerning toxicity and irritancy allow the use of animal tests to determine the presence of the hazard when human data or existing animal data are not available. However, the Commission's policy encourages manufacturers subject to the FHSA to use existing alternatives to animal testing wherever possible; supports limiting animal testing to a minimum number of animals; and advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. The Commission's

animal testing policy encourages manufacturers of products subject to the FHSA to use existing alternatives to animal testing, whenever possible, such as: prior human experience (*e.g.*, published case studies); *in vitro* or *in silico* test methods that have been approved by the Commission; literature resources containing the results of prior animal testing or limited human tests; and expert opinion. We believe that the animal testing policy codified at 16 CFR 1500.232, sufficiently communicates the preference for alternatives to animal testing, whenever possible, including the submission of relevant existing data resulting from prior animal testing.

Consideration of in Vitro Studies in Making Strong Sensitizer Determinations

Comment: One commenter asked why *in vitro* studies were added to the list of factors to consider in determining whether a substance is a strong sensitizer when such studies are not validated to determine potency. Another commenter requested that data from well-conducted *in vitro* assays be considered by the Commission in making this determination.

Response: The 1986 supplemental definition and the final rule definition both list *in vitro* data as a factor to be considered in determining whether a substance is a strong sensitizer. We agree that currently, there are no validated *in vitro* assays for sensitizer potency determination. However, a large number of *in vitro* assays are in development, undergoing validation, or have completed validation for the determination of sensitization. The European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM) completed validation of an *in vitro* assay and an *in chemico* assay this year. EURL-ECVAM recommended that neither assay could be used as a stand-alone test; although EURL-ECVAM determined that the assays could be included in a weight-of-evidence approach or integrated testing strategy. Although the assays

have some limitations, EURL-ECVAM concluded that with further work, these assays might be able to contribute to the assessment of sensitizer potency. As stated in the strong sensitizer guidance document, the CPSC would follow a weight-of-evidence approach, using all available validated tools (including both positive and negative data), in determining whether a substance is a strong sensitizer.

Consideration of Reports of Consumer Incidents

Comment: One commenter recommended including in the list of factors to be considered in determining whether a substance is a strong sensitizer, the CPSC's and manufacturers' records of incidents of consumer hypersensitivity to a substance or product containing a substance.

Response: We agree that incident reports are an important consideration in determining a substance's ability to cause hypersensitivity. The final rule definition lists "case histories" as information that the Commission may consider in determining whether a substance has a significant potential for causing hypersensitivity. The term "case histories" includes reports of incidents of consumer hypersensitivity to a substance or product containing the substance that are received by manufacturers or the CPSC. Commission staff will consider revising the Strong Sensitizer Guidance document to provide additional clarification regarding the types and sources of incident reports that CPSC should consider when determining whether a substance is a strong sensitizer.

Description of "Clinically Important Reaction"

Comment: The proposed definition provides that in determining whether a substance is a strong sensitizer, the Commission must consider the severity of the reaction to the substance and only designate substances as strong sensitizers that cause a "clinically

important reaction." The proposed definition includes a list of four potential reactions to strong sensitizer exposure that would be characterized as "clinically important" or manifestations of "substantial illness." One of the clinically important reactions listed in the proposed definition is "substantial physical discomfort or distress." One commenter noted that "discomfort and distress are actually perceptual (mental), although they may be caused by various agents (*e.g.*, physical, chemical agent, biological)." The commenter suggested replacing the phrase "substantial physical discomfort and distress" with the phrase "physiological stress resulting in discomfort or distress."

Response: We agree that the phrase "substantial physical discomfort or distress" may not be clear, but we believe that "physiological stress resulting in discomfort or distress," as suggested by the commenter, may also be too vague. We have replaced "substantial physical discomfort or distress" with "substantial physiological effects, such as discomfort and distress," as a factor to be considered in determining whether a strong sensitizer produces "substantial illness." We believe that this phrase reflects better a scenario such as a systemic allergic contact dermatitis rash.

Meaning of "Chronic Morbidity"

Comment: One commenter asked whether the reference to "chronic morbidity" as a factor in determining whether a strong sensitizer produces "substantial illness" was associated with a specific length of time, such as 90 days.

Response: The proposed definition includes a list of four potential reactions to strong sensitizer exposure that would be characterized as "clinically important" or manifestations of "substantial illness." One of the clinically important reactions listed in the proposed definition is "chronic morbidity." The Commission does not view the use

of the term "chronic" as referring to a specific length of time. Under the FHSA Chronic Hazard Guidelines (16 CFR 1500.135), which are broad guidelines containing a number of assumptions, methodologies, and procedures for determining chronic hazard and risk, the Commission does not set a length of time for "chronic," but instead, the Commission leaves the determination open to expert judgment. We have replaced the phrase "chronic morbidity" with "persistent morbidity" in the final rule definition to clarify that a "clinically important reaction" is a substantial illness that occurs over an extended period of time.

Addition of "Mortality" to "Substantial Illness" Factors

Comment: One commenter suggested that "mortality" be added to the list of factors to be considered in determining whether a strong sensitizer produces substantial illness.

Response: Mortality (*i.e.*, death) is not an illness but is a distinct endpoint that in rare cases could result from substantial uncontrolled anaphylaxis. We have revised the definition to include: "or in rare cases, mortality" at the end of the section that lists the types of reactions to substances that may be considered "substantial illness."

Removal of Oil of Bergamot from List of Strong Sensitizer Substances

Comment: One commenter requested that oil of bergamot (and products containing 2 percent or more of oil of bergamot) be removed from the list of "strong sensitizer" substances.

Response: Oil of bergamot is a phototoxin that FDA listed as a "strong sensitizer" (the list appears in 16 CFR 1500.13). The current rulemaking proceeding only addresses revisions to the supplemental definition of "strong sensitizer." To make any changes to

the existing list of substances currently considered to be strong sensitizers, the Commission would need to conduct a separate proceeding.

C. Revisions to the Strong Sensitizer Supplemental Definition

As discussed in Section B, above, the comments received in response to the NPR generally supported the Commission's replacement of the 1986 supplemental definition of "strong sensitizer" with the proposed definition. However, several commenters recommended additional changes that we have determined should be incorporated into the supplemental definition of strong sensitizer. Below, we discuss the differences between the 1986 supplemental definition and the proposed definition, along with the changes we have made to the proposed definition, based on comments and that have been incorporated into the final rule.

1. Definition of "Sensitizer" (§ 1500.3(c)(5)(i))

The 1986 supplemental definition specified that a "sensitizer" will "induce an immunologically-mediated (allergic) response, including allergic photosensitivity," that will become evident upon reexposure to the same substance, or occasionally, on first exposure, by virtue of active sensitization.

The final rule reflects the traditional definition for "sensitization"; sensitization is a multi-stage immune-mediated process that occurs over a period of time. Replacing the phrase "immunologically-mediated (allergic) response" with "immunologically-mediated hypersensitivity," captures those substances that sensitize through atypical mechanisms, rather than by inducing an obvious "immunologically-mediated response." The final rule also eliminates the last sentence of the current definition based on concerns that the sentence could be misinterpreted to include 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). Typically, allergic responses are the result of a two-step process: (1) induction (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 final rule includes the phrase "variable period of exposure" to reflect the latency period that is a characteristic in the development of sensitization. This section of the final rule is the same as proposed.

2. Determination of Significant Potential for Causing Hypersensitivity (§ 1500.3(c)(5)((ii))

The statutory definition of "strong sensitizer" requires that, before designating a substance as a strong sensitizer, the Commission "upon consideration of the frequency of occurrence and severity of reaction, shall find that the substance has a significant potential for causing hypersensitivity." 15 U.S.C. 1261(k).

As discussed in the NPR, the proposed definition added qualifiers for susceptibility profiles—genetics, age, gender, and atopic status— to the information and data listed in the 1986 supplemental definition that may be considered in determining whether a substance has a significant potential for causing hypersensitivity. These characteristics are well-known modifiers in the development and exacerbation of allergic responses to chemical sensitizers. In response to a comment, for the final rule, we have reordered the list as it appeared in the proposed definition so that the final definition presents the factors to be considered in determining whether a substance has a significant

[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.

potential for causing hypersensitivity. This represents the same order as the factors to be considered in determining whether a substance is a "strong" sensitizer. This reordering results in "chemical or functional properties of the substance" becoming the last category on the list, and the references to *in vitro* and *in vivo* experimental studies are reversed.

As discussed in the NPR, the proposed definition also replaced the term "normal" with "non-sensitized," which describes more accurately the general control population. This remains the same in the final rule.

As discussed in the NPR, the proposed definition incorporated the factors to be considered in determining whether a substance is a "strong" sensitizer into the subsection explaining "significant potential for causing hypersensitivity." The 1986 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)). This section of the 1986 supplemental definition 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.

As discussed in the NPR, the proposed definition eliminated the "quantitative or qualitative risk assessment factor. " We believe this terminology is confusing because the language places a risk assessment step within the hazard identification step of the process of determining whether a product containing a strong sensitizer is a hazardous substance that requires labeling. The NPR proposed definition remains the same in the final rule, except for the reordering of certain factors in response to a comment.

As discussed in the NPR, the proposed definition 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 allow an "any or all" approach to the factors that would be considered by the Commission in determining whether a sensitizer is strong, the revision ranks data sources in order of importance following the FHSA preference for human data over animal data and 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 definition expressed 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 ranking of data sources remains the same in the final rule.

As discussed in the NPR, the proposed definition listed additional factors that 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 have revised the definition in the final rule to reposition these factors from the end of

[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.

Section 1500.3(c)(5)(ii) to follow immediately the listing of ranked factors that are to be considered in determining whether a substance is a "strong" sensitizer.

As discussed in the NPR, the proposed definition provided 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. The Commission has revised the proposed definition in response to a comment to replace "substantial physical effects" with "substantial physiological effects" as a factor to be considered in determining whether a strong sensitizer produces "substantial illness"; to replace "chronic morbidity" with "persistent morbidity"; and to add "or in rare cases, mortality" to the end of section 1500.3(c)(5)(ii). The change from "physical" to "physiological" is intended to describe more accurately and broadly the body's response to exposure to a substance that could rise to the level of a clinically important reaction. The change from "chronic" to "persistent," also made in response to a comment, is intended to convey more clearly that a substantial illness may be one that endures for an extended period of time.

As discussed in the NPR, the proposed definition also directed 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." This aspect of the NPR remains the same in the final rule.

3. Definition of Normal Living Tissue (§ 1500.3(c)(5)(iii))

The statutory definition of "strong sensitizer" specifies that a strong sensitizer is a substance that will cause hypersensitivity on "normal living tissue." The 1986

supplemental definition identifies skin and other organ systems, such as the respiratory or gastrointestinal tract, as types of "normal living tissue" in which the allergic hypersensitivity reaction can occur. The proposed definition adds a specific reference to mucous membranes, such as ocular and oral systems, as additional types of normal living tissue upon which a substance can cause a hypersensitivity that warrants a determination that a substance is a "strong sensitizer." This remains the same in the final rule.

D. Staff Guidance and Notice of Availability

Commission staff 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 was published in the *Federal Register* on March 12, 2013 (78 FR 15710), which provided a link to the location on the Commission's website where the staff guidance document can be found. Several commenters included questions and observations regarding the guidance document in their submissions addressing the proposed revision to the definition of "strong sensitizer." Commission staff will review these comments, and where appropriate, will revise the guidance document.

E. Impact on Small Businesses

The Commission certifies that this rule will not a have a significant impact on a substantial number of small entities under section 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 605(b). For the NPR, the Commission's Directorate for Economic Analysis prepared an assessment of the impact of the proposed definition of "strong sensitizer." That assessment found that there would be little or no effect on small

businesses and other entities because the amendment, which simply modifies the existing supplemental definition of "strong sensitizer," will not result in compliance actions. Products will not need to be modified to comply with the revised supplemental definition, 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 particular substance contained in the product as a strong sensitizer, which would occur only in connection with a separate process. Thereafter, we would assess the potential small business impact of designating the particular substance as a strong sensitizer. Whether the final rule would impose any indirect burden on small businesses or other entities is unknown because the impact of the changes to the supplemental definition of strong sensitizer on future strong sensitizer designation proceedings is not known. The Commission did not receive any comments concerning the impact the rule would have on small businesses and is not aware of any information that would alter the assessment stated in the NPR.

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 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 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). The final rule will take effect 30 days after publication 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 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. 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: 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.

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).

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 physiological effects, such as discomfort and distress, substantial hardship, functional or structural impairment, 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.

Dated:_____

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

Staff Briefing Package

Revised Supplemental Definition of "Strong Sensitizer"
Draft Final Rule
January 29, 2014

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Briefing Memorandum

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

Memorandum

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Stephanie Tsacoumis, General Counsel
Elliot F. Kaye, Executive Director
Robert J. Howell, Deputy Executive Director for Safety Operations

FROM : George A. Borlase, Ph.D., P.E., Assistant Executive Director, Office of Hazard Identification and Reduction
Joanna M. Matheson, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT : Draft Final Rule: Revision of the Strong Sensitizer Supplemental Definition

Introduction

"Strong sensitizer" is one of the seven categories of hazards defined under the Federal Hazardous Substance Act (FHSA). The following statutory definition of the term "strong sensitizer" 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.

The authority to administer the FHSA resided with the U.S. Food and Drug Administration (FDA) until that authority was transferred to the U.S. Consumer Product Safety Commission (CPSC, Commission) in 1973, shortly after the creation of CPSC in 1972. During the time that CPSC has administered the FHSA; the Commission has not designated any substances to be strong sensitizers. In 1986, the Commission issued a rule clarifying the FHSA's "strong sensitizer" definition with a supplemental definition, as recommended by a Technical Advisory

Panel on Allergic Sensitization.[1] The 1986 strong sensitizer supplemental definition was intended to clarify how the statutory definition should be interpreted in view of the current scientific knowledge, and the definition listed the factors the Commission would consider in determining whether a substance is a strong sensitizer.

Recognizing that the science on sensitization had changed since the 1986 supplemental definition was published, CPSC staff, in 2005, convened an international panel of scientific experts from academia, industry, and the federal government. CPSC convened the panel of experts to examine the available scientific and medical information concerning sensitizers, and if deemed appropriate, to propose revisions to the supplemental definition of "strong sensitizer." In 2006, based on the expert panel's input, CPSC staff developed and sought public comment on a draft technical report proposing revisions to the supplemental definition.[2]

In 2007, the technical report underwent U.S. federal agency peer review by staff from the Centers for Disease Control and Prevention's 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. CPSC staff addressed the federal agency peer review comments in a draft technical report; and in late 2007, the draft technical report underwent external scientific peer review. The external peer reviewers were tasked with evaluating CPSC staff's draft technical report and the report's appendices and assessing whether the report reflected the current state of the science with regard to determining when a substance is a strong sensitizer. In 2008, CPSC staff revised and updated the draft technical report, taking into consideration the comments from the external peer review.

Notice of Proposed Rulemaking

Based upon the public and peer review comments, in 2008, staff drafted a revision of the supplemental definition of the term "strong sensitizer." In February 2013, staff provided the Commission with a briefing package recommending certain revisions to the supplemental definition: http://www.cpsc.gov/Global/Newsroom/FOIA/CommissionBriefingPackages/2013/strongsensitizer.pdf). On March 12, 2013, the Commission published a notice of proposed rulemaking (NPR), proposing to revise the FHSA supplemental definition of "strong sensitizer," as staff had recommended.[3] Staff believed that the proposed revision eliminated redundancy; removed subjective factors; incorporated new and future technology that will be available within the next 5 years; ranked the criteria for classification of strong sensitizers in order of importance (*e.g.*, human over animal data); defined criteria for "severity of reaction" (which is undefined in the existing definition and is a critical consideration for declaration of a "strong sensitizer"); and

[1] The strong sensitizer supplemental definition is found at 16 C.F.R. § 1500.3(c)(5). CPSC revoked the original supplemental definition in 1984 because the supplemental definition was narrower than the statutory definition. In addition, the advisory panel and CPSC staff believed that the supplemental definition did not account for the different paths in which an individual can become sensitized.

[2] The technical report (located at: www.cpsc.gov/PageFiles/111703/StrongSensitizer.pdf) summarizes the responses from the scientific panel to a series of questions regarding the "strong sensitizer" supplemental definition. The technical report also provides a rationale for the proposed modifications to the existing supplemental definition.

[3] Found at Federal Register, Vol. 78, No. 48, 15660: http://www.regulations.gov/#!documentDetail;D=CPSC-2013-0010-0001.

indicated that a weight-of-evidence approach[4] will be used in the determining whether a substance is a "strong sensitizer." Staff also prepared a guidance document describing the factors staff considers when evaluating consumer products that could contain a strong sensitizing substance. Staff posted this guidance document on the CPSC's website at: http://www.cpsc.gov/global/regulations-laws-and-standards/regulated-products-rules/strongsensitizerguidance.pdf. When the Commission approved publication of the NPR proposing the revised definition of "strong sensitizer," the Commission also approved publication of a notice in the *Federal Register* announcing the availability of staff's guidance document.[5]

Public Comments

The NPR requested comments on the proposed revisions to the supplemental definition of "strong sensitizer." [6] The CPSC received comments on the proposed rule from the following stakeholders: a consulting toxicologist; the International Fragrance Association of North America; the International Science Consortium of the People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine; the American Chemistry Council; and the Diisocyanates Panel of the American Chemistry Council (see Tab C for the list of the Commenters and their briefing package identifying number).

All commenters were generally supportive of a rule revising the supplemental definition of "strong sensitizer." Specifically, the commenters agreed with the following aspects of the NPR proposed revisions:

- removing the language in the definition of "sensitizer," that states that, occasionally, a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization, to minimize the potential for irritant responses being characterized as sensitization responses (commenters 2, 3, 4; see page 14 of the NPR briefing package for a discussion on the proposed change[7]);
- revising the definition of "sensitizer" to state that sensitization is an immunologically mediated, multistage process, that occurs over a period of time (commenter 3; see page 14 of the NPR briefing package for a brief discussion on the proposed change);
- recognizing in the revised definition of "normal living tissue" that other tissues beyond the skin and respiratory system could have allergic responses (commenter 2; ; see page 18 of the NPR briefing package for a brief discussion on the proposed change);

[4] Weight-of-evidence is an evidence-based approach that involves an assessment of the relative values/weights of all available information. The approach considers 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.
[5] The notice announcing the availability of staff's guidance document is available in the docket at: http://www.regulations.gov/#!documentDetail;D=CPSC-2013-0010-0002.
[6] The NPR and public comments are available in the docket at: http://www.regulations.gov/#!documentDetail;D=CPSC-2013-0010-0001.
[7] More extensive discussion on proposed revisions to the "strong sensitizer" supplemental definition can be found in the 2008 strong sensitizer technical report located at: www.cpsc.gov/PageFiles/111703/StrongSensitizer.pdf.

- recognizing the importance of developing and considering *in vitro* and *in silico* test studies[8] and the importance of determinations relating to clinically relevant sensitization reactions being based on reliable, predictive techniques, such as those listed in the revised supplemental definition (commenter 3; see pages 15 and 16 of the NPR briefing package for a brief discussion on the proposed change);
- staff's opinion that the proposed supplemental definition is more in line with international criteria (commenter 5); and
- including frequency of occurrence and range of severity of reactions as considerations in making a "strong sensitizer" determination (commenter 3).

Three of the commenters suggested revisions to staff's guidance document, "Strong Sensitizer Guidance." CPSC staff will consider the input provided by commenters as the basis for possible revisions of the guidance document in the future.

Below, staff summarizes and responds to specific issues raised by the comments to the NPR.

Harmonization with International Criteria

Comment: Two commenters (commenters 4, 5) recommended that the Commission take additional action to harmonize "strong sensitizer" criteria with international criteria, in particular, encouraging the Commission to implement the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).[9] One commenter requested that if the Commission adopts the GHS, the Commission still adhere to the FHSA mandates for risk-based decision making for hazards covered under the FHSA.

Response: CPSC staff has been, and continues to be, actively involved in the development of the GHS. As stated in the agency's policy statement on the GHS: "as the Commission moves forward with its role in implementation of the GHS, the Commission will adhere to the mandates for risk-based decision making of the Consumer Product Safety Act, Federal Hazardous Substances Act, Flammable Fabrics Act, and Poison Prevention Packaging Act. In particular, with respect to the labeling of chronic health hazards in the consumer product setting, the Commission intends to follow the risk-based labeling option specified under Annex 5 of the GHS." The GHS bases its hazard classifications on the inherent hazard of a substance, while the FHSA, with its risk-based decision making, takes into consideration exposure, along with the intrinsic hazard of the substance. The GHS Annex 5, "Consumer Product Labelling Based on the Likelihood of Injury," was developed to recognize CPSC risk-based decision making. Annex 5 provides certain general principles, including that "risk-based labelling can only be applied by the competent authorities to the chronic health hazards of chemicals in the consumer product setting." Annex 5 references the FHSA two-part process: the first step is the performance of a

[8] *In silico* data represent a computational approach, *i.e.*, using sophisticated computer models rather than animals or *in vitro* (cell-culture based) tests, to determine sensitizing potential.

[9] 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 is 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 a standard. The GHS establishes agreed-upon hazard classification and communication criteria with explanatory information on how to apply the system.

hazard assessment; and the second part is a risk assessment carried out to establish whether a substance has the potential to cause substantial illness or injury during, or as a result of, reasonably foreseeable handling or use or from ingestion by children. The CPSC GHS policy statement can be found at: http://www.cpsc.gov/en/About-CPSC/Policies-Statements-and-Directives/Policy-of-the-US-Consumer-Product-Safety-Commission-on-the-Globally-Harmonized-System-of-Classification-and-Labeling-of-Chemicals-GHS/.[10]

Effect of Rule on Regulation of Products and Risk Management Actions

Comment: Commenter 5 stated that CPSC's proposal could have far-reaching effects on the regulation of products on a broader level; specifically, classifying substances as "strong sensitizers" may prompt risk-management actions by CPSC or other regulatory bodies, the commenter asserted. The commenter encouraged the CPSC to ensure that classification determinations fully reflect a science- and risk-based approach that considers the degree of hazard and extent of exposure potential.

Response: The draft rule does not designate any particular substance as a "strong sensitizer"; but the draft rule revises the regulatory definition of "strong sensitizer." Staff does not believe that revising this definition will have "far-reaching effects." Under the FHSA, labeling or other regulatory action is required only when a substance meets the definition of "hazardous substance." The determination that a substance is a "strong sensitizer," by itself, does not require any action by a manufacturer. The strong sensitizer would have to meet the rest of the definition of "hazardous substance" (15 U.S.C. § 1261(f)) to be declared a hazardous substance and be subject to risk management actions. A substance that the Commission designates as a "strong sensitizer" could be a "hazardous substance" under the FHSA, "if such substance or mixture of substances may cause 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." Therefore, by definition, the FHSA considers exposure and requires a case-by-case hazard assessment. The revised supplemental definition reflects both a science- and risk-based approach, such that the decision for classification is not based solely on a product's ingredients.

Description of "Strong Sensitizer" Determination Process

Comment: Commenters 4 and 5 suggested that the CPSC clearly describe the administrative process used to make the determination that a substance or product containing a substance is a strong sensitizer so that stakeholders will be aware of their opportunities for participation in the process.

Response: Under the FHSA, the Commission must first designate a substance a "strong sensitizer" for the substance to be considered a "strong sensitizer," (15 U.S.C. § 1261(k)). Such a designation would occur in a separate proceeding which is outside the scope of this action. The

[10] All sections of the GHS including Annex 5 can be found at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev05/05files_e.html.

current action relates only to the regulatory definition, not to designation of a particular substance as a strong sensitizer

Labeling Requirement for "Strong Sensitizers"

Comment: Commenter 4 requested guidance regarding circumstances that would not trigger a labeling requirement for products containing a strong sensitizer.

Response: As discussed in response to comments above, Commission action would be necessary to designate a particular substance a "strong sensitizer." As stated in 15 U.S.C. § 1261(k), labeling would be required only if the Commission designated a substance to be a "strong sensitizer" **and** if the substance met the remaining portions of the FHSA definition of "hazardous substance." That is, under the FHSA definition (as stated at 15 U.S.C. § 1261(f)), a "hazardous substance" is one that is a "strong sensitizer" (or has another of the specified "hazardous substance" characteristics) **and** "may cause 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." Thus, manufacturers of products containing a strong sensitizer would have to determine whether the concentrations and availability of the substance in their products could cause substantial injury or illness as a result of reasonably foreseeable handling or use. A hazardous substance that is not properly labeled with appropriate cautionary statements in accordance with section 2(p) of the FHSA (see 15 U.S.C. § 1261(p)) is considered a "misbranded hazardous substance." Introducing, delivering for introduction, or receiving in interstate commerce a misbranded hazardous substance is a prohibited act (see 15 U.S.C. § 1263(a) and (c)). The Commission also has the option of issuing a rule under Section 3(a) of the FHSA specifically to designate an item as a hazardous substance to reduce uncertainty about which products would be considered a hazardous substance (see 15 U.S.C. § 1262(a)(1)).

Separate Treatment of Type I and Type IV Allergies in "Strong Sensitizer" Supplemental Definition

Comment: Commenter 3 requested that Type I and Type IV allergies be considered separate categories in the proposed supplemental definition of the term "strong sensitizer" because the different potential for illness, discomfort, and morbidity between these two allergy types could require the use of completely different types of data. The commenter stated that the evaluation of data leaves the assessment to subjective judgment that could be highly variable.

Response: Staff agrees that evaluating whether a substance is a strong sensitizer will depend on the substance and the allergic response the substance induces. However, staff believes that the revised supplemental definition would be significantly more complex if these two types of allergies were separated into distinct categories. Criteria would need to be established distinguishing the two different immunologically-mediated mechanisms of sensitization, likely resulting in a lengthier, potentially less clear, supplemental definition.

The revised supplemental definition includes the various potential routes of exposure as well as the anatomic sites of an allergic response. The outcome of exposure, whether it is a dermal or

respiratory response, will likely require different data for evaluation because evaluating whether a substance is a strong sensitizer requires a case-by-case inquiry based on high-quality relevant data. The staff's guidance document explains the approach staff would take in evaluating these two classes of allergy and believes that the criteria in the revised supplemental definition provide the flexibility for assessing these two classes of allergy without the need for specifically differentiating them.

Ordering of Factors to be Considered in Determining Whether a Substance has Significant Potential for Causing Hypersensitivity

Comment: Commenter 1 agreed with staff's proposed supplemental definition that human data should appear first in the list of factors taken into consideration in determining whether a substance is a "strong sensitizer", using a weight-of-evidence approach. However, the commenter suggested revising the order of the other factors, as well as including unranked data that appear in other sections of the supplemental definition. The commenter's requested revision would: (1) shift the order of factors other than human data; (2) move unranked factors to ranked factors (quantitative structure-activity relationship information, bioavailability data, information on frequency of occurrence and severity of reaction); (3) and separate into different categories existing versus new *in vitro* and *in vivo* studies, as follows: [11]

> "(A) well-conducted clinical and diagnostic studies;
> (B) epidemiological studies, with a preference for general population studies over occupational studies;
> (C) quantitative structure-activity relationship (QSAR)[12] information;
> (D) bioavailability data[13] ;
> (E) information pertaining to the frequency of occurrence and severity of reaction;
> (F) existing historical data from *in vivo* or *in vitro* studies;
> (G) *in vitro* test studies;
> (H) cross-reactivity data[14] ;
> (I) case studies;
> (J) animal studies."

Response: Staff believes that the list of criteria should remain as stated in the revised supplemental definition proposed in the NPR. The criteria list reflects Commission policy that human data take precedence over animal data. The criteria list is also consistent with the CPSC Animal Testing Policy, the FHSA Chronic Hazard Guidelines, international guidelines, and Commission policy that strongly encourage the use of scientifically validated alternatives to

[11] The commenter's list of ranked factors is missing "(E)"; therefore, the commenter's list of factors was shifted up one position in this briefing memorandum.
[12] QSARs are mathematical models that relate a quantitative measure of chemical structure to biological activity.
[13] Bioavailability as defined in the supplemental definition 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.
[14] Cross-reactivity is the reaction between an antigen and an antibody that was generated against a different but similar antigen. Therefore, allergic cross-reactivity occurs when there is structural similarity between allergens, one that an individual was exposed to and a structurally-similar allergen the individual did not have previous exposure to.

animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results.[15]

Staff based the order of data criteria on extensive input from the 2005 international panel of scientific experts from academia, industry, and the federal government (a discussion on the ranked criteria can be found on pages 75 and 76 in the 2008 strong sensitizer technical report located at: www.cpsc.gov/PageFiles/111703/StrongSensitizer.pdf). The list of criteria is as follows:

(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.

CPSC staff concurred with the panelists' suggestion to list the qualifying factors in order of importance, instead of "any or all," which is how the factors appear in the current 1986 supplemental definition. Staff also ranked the criteria based on the ability of the data to be used as stand-alone data, along with the strength and relevance of the data, for determining whether a substance has a significant potential for causing hypersensitivity.

The commenters placed frequency of occurrence and severity of response as criteria "E". This placement minimizes the consideration of the prevalence and severity of an allergic response, and is in conflict with the strong sensitizer statutory definition. Before deciding whether a substance is a strong sensitizer, and upon the determination of whether a substance has significant potential for causing hypersensitivity, the Commission *is required* to consider the prevalence of sensitization (frequency of occurrence) and severity of response.

Use of Existing Animal Testing Data

Comment: Commenter 1 recommended that CPSC request that existing animal testing data be submitted before any additional animal data are generated.

Response: Although 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, if the product is or contains a hazardous substance. As stated in the CPSC Animal Testing Policy, codified at 16 C.F.R. § 1500.232 (77 FR 73286), neither the FHSA, nor the regulations issued thereunder, requires animal testing to determine whether a hazard exists. The CPSC has amended and updated its animal testing regulations to allow alternatives to animal testing whenever possible. Under the FHSA, animal testing is one possible option that can be used to determine the biological response to a "strong sensitizer" and the appropriate cautionary labeling.

[15] Discussion on the ranking of the criteria can be found on pages 10, 15 and 16 of the NPR briefing package (found at http://www.cpsc.gov/Global/Newsroom/FOIA/CommissionBriefingPackages/2013/strongsensitizer.pdf).

The Commission's policy is to encourage manufacturers subject to the FHSA to (1) find alternatives to traditional animal testing, (2) reduce the number of animals tested, and (3) decrease the pain and suffering in animals associated with testing household products. Although CPSC does not specifically request that existing animal testing data be submitted before any additional animal data are generated, the Commission and CPSC staff, in accordance with the agency's animal testing policy, strongly encourage the use of scientifically validated alternatives to animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results, in the determination of hazard for all potential hazardous substances, including, but not limited to, strong sensitizers, irritants and toxins. The CPSC Animal Testing Policy can be found at: http://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/ and http://www.cpsc.gov/PageFiles/134753/animaltestfinalfr.pdf.

Acceptance of Data from Certain QSAR Models

Comment: Commenter 1 requested that the supplemental definition be revised to provide for the acceptance of data from QSAR models that have been evaluated and approved by the Organisation for Economic Co-operation and Development (OECD) for specific applicability domains.

Response: The revised supplemental definition specifically states that in determining whether a substance has a significant potential for causing hypersensitivity, chemical or functional properties of the substance of interest, in addition to QSAR data, can be considered. The CPSC international panel of experts and external peer reviewers determined that QSAR data are not sufficient as stand-alone analyses for determining potency of a sensitizer but that QSAR analysis could be used in a weight-of-evidence approach.

The OECD Council Act relating to the Mutual Acceptance of Data (MAD), which was agreed to by all OECD member countries, established that safety data developed in one member country will be accepted for use by the relevant registration authorities in assessing the chemical or product in another OECD country (*i.e.*, the data do not have to be generated a second time for the purposes of safety assessment), under the assurance that the data were developed in compliance with the Principles of Good Laboratory Practice. Therefore, if a manufacturer submits QSAR data to the Commission when the Commission is determining whether a substance is a strong sensitizer, the Commission will take the QSAR data into consideration. However, this QSAR data will not take precedence over high-quality human and animal data. Staff believes that the revised supplemental definition should not be modified in response to this comment.

Consideration of *In Vitro* Studies in Making Hypersensitivity Determinations

Comment: Commenter 4 asked why *in vitro* studies were added to the list of factors to consider when such studies are not validated to determine potency. In addition, another commenter (commenter 1) asked that data from well-conducted *in vitro* studies be considered.

Response: The current strong sensitizer supplemental definition includes consideration of *in vitro* data. Staff agrees that currently there are no validated *in vitro*, as well as *in chemico*[16] and *in silico*, assays for sensitizer potency determination. However, a large number of assays are either in development, undergoing validation, or have completed validation for the determination of sensitization. The European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM) completed validation of two assays (an *in vitro* assay and an *in chemico* assay) this year. EURL-ECVAM recommended that neither assay could be used as a stand-alone test; although EURL-ECVAM determined that the assays could be included in a weight-of-evidence approach or integrated testing strategy. Although the assays have some limitations, EURL-ECVAM concluded that with further work, these assays might be able to contribute to the assessment of potency. As stated in the strong sensitizer guidance document, the CPSC would consider multiple factors before concluding 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 and all available data (including both positive and negative data). Existing human data are preferred by CPSC over animal data, with quality of data taken into consideration.

Consideration of Reports of Consumer Incidents

Comment: Commenter 2 recommended including in the list of factors indicated in the weight-of-evidence approach, CPSC's and manufacturers' records of incidents of consumer hypersensitivity to a substance or product containing a substance.

Response: Staff agrees that incident reports are an important consideration in determining a substance's ability to cause hypersensitivity. Staff believes that the term "case histories" in the criteria list will provide for the consideration of manufacturers' records of consumer incidents and CPSC incident reports in determining whether a substance has a significant potential for causing hypersensitivity. Staff will consider revising the strong sensitizer guidance document to clarify what incident reports should be considered.

Description of "Clinically Important Reaction"

Comment: Commenter 2 stated: "discomfort and distress are actually perceptual (mental), although they may be caused by various agents (*e.g.*, physical, chemical agent, biological)." The commenter suggested replacing "substantial physical discomfort and distress" with "physiological stress resulting in discomfort or distress."

Response: The current and proposed supplemental definition lists examples of what may constitute substantial illness. One example is "substantial physical discomfort and distress." Staff agrees that the reference to "physical" may not be clear, but is concerned that "physiological stress," as suggested by the commenter, may also be too vague. Therefore, staff recommends that the Commission revise the supplemental definition to reference "substantial physiological effects, such as discomfort and distress," as a factor to be considered in determining whether a strong sensitizer produces "substantial illness." Staff believes that this phrase better reflects scenarios such as a systemic allergic contact dermatitis rash.

[16] *In chemico* methods are physicochemical reactivity methods that do not contain biological material (abiotic).

Criteria of "Chronic Morbidity"

Comment: Commenter 2 asked whether the reference to "chronic morbidity" as a factor in determining whether a strong sensitizer produces "substantial illness" was associated with a specific length of time, such as 90 days.

Response: The current and revised supplemental definition lists examples of "substantial illness." One example is "chronic morbidity." Staff does not assign a specific length of time with this use of "chronic." Under the FHSA Chronic Hazard Guidelines (found at 16 C.F.R. §1500.135), which are broad guidelines containing a number of assumptions, methodologies, and procedures for determining chronic hazard and risk, the Commission has not set a length of time for "chronic," but instead, leaves the determination open to expert judgment. However, other federal agencies have a defined length of time for "chronic." Therefore, staff recommends that the Commission change the revised supplemental definition to replace "chronic morbidity" with "persistent morbidity" to reflect staff's intention of defining an extended period of substantial illness.

Addition of "Mortality" to "Substantial Illness" Factors

Comment: Commenter 2 suggested that "mortality" be added to the list of factors to be considered in determining whether a strong sensitizer produces substantial illness.

Response: The current and revised supplemental definitions list examples of what may constitute substantial illness. Mortality (*i.e.*, death) is not an illness but is a distinct endpoint and, in rare cases, could result from substantial uncontrolled anaphylaxis. Staff, therefore, recommends that the Commission revise the proposed definition to include "or in rare cases, mortality" at the end of the sentence providing examples of what may constitute substantial illness.

Consistency of Order of Factors Listed Throughout the Rule

Comment: Commenter 4 pointed out that the factors for consideration of *"significant potential for causing hypersensitivity"* were not listed in the same order when listed as factors to be considered in determining whether a substance is a "strong sensitizer." Thus, the commenter requested that the Commission be consistent in the priority ranking of data between these two sections.

Response: Staff agrees with the commenter that the priority ranking of factors should be consistent between these sections. Staff recommends that the Commission revise the proposed definition as follows:

- in the first paragraph of section (*ii*), move "chemical or functional properties of the substance" to the end of the paragraph's last sentence;
- in the same sentence as above, reverse the positions of *in vitro* and *in vivo;* and
- move the paragraph that includes consideration of Quantitative Structure-Activity Relationships, *in silico* data, and specific human sensitization threshold values, so that the

paragraph is positioned immediately below the ranked factors that should be considered in the determination of whether a substance is a strong sensitizer.

Removal of Oil of Bergamot from List of "Strong Sensitizer" Substances

Comment: Commenter 3 requested that oil of bergamot (and products containing 2 percent or more) be removed from the list of "strong sensitizer" substances.

Response: Oil of bergamot is a phototoxin that FDA placed in the listing of "strong sensitizer" substances that appears in 16 C.F.R. §1500.13. The current rulemaking proceeding only addresses revisions to the supplemental definition of "strong sensitizer." The Commission would be required to conduct a separate rulemaking to make any changes to the list of substances currently considered to be strong sensitizers.

Staff's Recommendations for Final Supplemental Definition of "Strong Sensitizer"

Based on the comments submitted, staff recommends several changes to the revised supplemental definition that the Commission proposed in the NPR. Staff discusses the reasons for suggesting these changes in the response to comments section above. These changes include: wording changes in the list of examples of what may constitute substantial illness (*e.g.*, "chronic" should be replaced with "persistent"; "physical" should be changed to "physiological": and "or in rare cases, mortality" should be added). In addition, staff recommends changing the order of the consideration criteria (*e.g.*, moving "chemical or functional properties of the substance" to the end of the sentence; moving *in vivo* so that it appears before *in vitro* in the sentence) so that the ranking order is consistent throughout the *"significant for causing hypersensitivity"* section. Staff also recommends changing "individual case studies" to "case histories" to have consistent language used throughout the supplemental definition. Staff recommends that the Commission issue a final rule revising the supplemental definition of "strong sensitizer" to state the following:
(changes from the proposed rule appear in **bold type**, red strikeouts indicate what is deleted; Tab A contains the unmarked proposed final supplemental definition)

(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. The determination may be based on ~~chemical or functional properties of the substance~~; documented medical evidence of hypersensitivity reactions upon subsequent exposure to the same substance that is obtained from epidemiological surveys or **case histories** ~~individual case studies~~; controlled ***in vivo*** ~~*in vitro*~~ or ***in vitro*** ~~*in vivo*~~ 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.

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).

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** ~~physical~~ effects, such as discomfort and distress;
(B) substantial hardship;
(C) functional or structural impairment;
(D) **persistent** ~~chronic~~ morbidity;

or in rare cases, mortality.

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.

Staff Conclusions

CPSC staff recommends that the Commission approve the draft final rule amending 16 C.F.R. part 1500 so that the revised supplemental definition of "strong sensitizer" aligns with current scientific and medical knowledge.

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 recommended changes to the strong sensitizer supplemental definition do not place any additional requirements on manufacturers (Tab B). Instead, the revised supplemental definition clarifies 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 will align more closely with internationally harmonized criteria for sensitizing substances.[17]

[17] 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, the option of declaring substances to be strong sensitizers 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.

TAB A: Revised Strong Sensitizer Supplemental Definition

TAB A

The statement below represents staff's recommendations for the final "strong sensitizer" supplemental definition, including changes made in response to comments from the public.

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. 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.

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).

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.

TAB B: Regulatory Flexibility Act Analysis

TAB B

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

Memorandum

Date: DRAFT November 5, 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 Final Rule Revising the Supplemental Definition of "Strong Sensitizer": Potential Impact on Small Firms

This memorandum discusses the potential impact of the draft final rule revising the supplemental regulatory definition of "strong sensitizer." The revisions to the regulatory definition of "strong sensitizer" are intended to make the definition more consistent with current scientific knowledge and more consistent with the Globally Harmonized System of Classification and Labeling of Chemicals.

The Commission published a notice of proposed rulemaking (NPR) to revise the definition of a "strong sensitizer" in the Federal Register of March 12, 2013. The NPR contained an assessment of the potential impact of the proposed rule on small entities. That assessment concluded that the proposed rule would have little or no effect on small businesses and other entities because the rule would not impose any direct burden on any small business or other entity. The obligation of a business to test and label products for the presence of a strong sensitizer occurs only after the Commission has designated a substance as a strong sensitizer and only if the product meets the rest of the definition of "hazardous substance" under the Federal Hazardous Substances Act (FHSA). The designation of a substance as a strong sensitizer requires a separate rulemaking procedure, and any analysis of the impact on small businesses of the designation of a particular substance as a strong sensitizer would be assessed at that time. Moreover, whether there would be any indirect impact is not known because the impact of the amendments in future proceedings concerning "strong sensitizers" is not known. Based upon this assessment, the Commission found preliminarily that the proposed rule would not have a significant impact on a substantial number of small entities.

The Commission did not receive any public comments that challenged the preliminary finding that the revisions would not have a significant impact on a substantial number of small entities; neither has Commission staff become aware of any information after publication of the NPR that causes the staff to question the agency's earlier conclusion. Therefore, staff believes that the Commission can certify that the draft final rule revising the supplemental regulatory definition of "strong sensitizer" will not have a significant impact on a substantial number of small entities.

TAB C: Identification of NPR Commenters

TAB C

Identification of NPR Commenters

Commenter number	Comment identification	Commenter	Organization
1	CPSC-2013-0010-0004	Amy Clippinger	PETA International Science Consortium
2	CPSC-2013-0010-0005	Brian C. Lee	Good Afternoon Toxicology Consulting, LLC
3	CPSC-2013-0010-0006	Megan Ekstrom	International Fragrance Association North America
4	CPSC-2013-0010-0007	Sahar Osman-Sypher	American Chemistry Council, Diisocyanates Panel
5	CPSC-2013-0010-0008	Brendon Mascarenhas	American Chemistry Council

Note: The public comments may be found in docket CPSC-2013-0010 at:
http://www.regulations.gov/#!documentDetail;D=CPSC-2013-0010-0001