UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
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BETHESDA, MD 20814

This document has been electronically approved and signed.

BALLOT VOTE SHEET

Date: November 19, 2012

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Mary T. Boyle, Acting General Counsel
Kenneth R. Hinson, Executive Director

FROM : Patricia M. Pollitzer, Assistant General Counsel
Hyun S. Kim, Attorney, OGC

SUBJECT : Final Rule on Revisions to Animal Testing Regulations; Final Codification of Animal Testing Policy

BALLOT VOTE Due: November 26, 2012

Attached are the following draft *Federal Register* notices for Commission consideration: (A) Final Rule on Revisions to Animal Testing Regulations; and (B) Final Codification of Animal Testing Policy.

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

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

_____ _____
(Signature) (Date)

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

_____

_____

_____

_____ _____
(Signature) (Date)

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

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

_____

_____

_____

_____ _____
(Signature) (Date)

B. Please indicate your vote on the following options on the final codification of animal testing policy:

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

_____ _____
(Signature) (Date)

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

_____

_____

_____

_____ _____
(Signature) (Date)

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

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

_____

_____

_____

_____ _____

(Signature) (Date)

Attachments: Draft *Federal Register* notices: (1) Final Rule on Revisions to Animal Testing Regulations; (2) Final Codification of Animal Testing Policy

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

[CPSC Docket No. CPSC-2012-0036]

16 CFR Part 1500

Hazardous Substances and Articles; Administration and Enforcement Regulations: Revisions to Animal Testing Regulations

AGENCY: Consumer Product Safety Commission.

ACTION: Final Rule

SUMMARY: The U.S. Consumer Product Safety Commission (CPSC or Commission) amends regulations on the CPSC's animal testing methods under the Federal Hazardous Substances Act (FHSA).

DATES: This rule is effective on **[insert date that is 30 days after publication in the Federal Register**].

FOR FURTHER INFORMATION CONTACT: Leslie E. Patton, Ph.D., Project Manager, Office of Hazard Identification and Reduction, U.S. Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7848; lpatton@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

The Federal Hazardous Substances Act (FHSA), 15 U.S.C. 1261–1278, requires appropriate cautionary labeling on certain hazardous household products to alert consumers to the potential hazards that a product may present. Among the hazards addressed by the FHSA are products that are toxic, corrosive, irritants, flammable,

combustible, or strong sensitizers. The FHSA and the Commission regulations at 16 CFR part 1500 provide certain definitions and test methods related to testing on animals to determine the existence of the hazards addressed by the FHSA.

On June 29, 2012, the Commission issued a notice of proposed rulemaking to amend and to update regulations on the CPSC's animal testing methods under the FHSA. 77 FR 38754. The Commission proposed amendments to the regulations that interpret, supplement, or provide alternatives to definitions of animal test methods used to aid in the classification of hazardous substances under the FHSA.

In addition, on June 29, 2012, the Commission proposed to codify its statement of policy on animal testing to reflect new methods accepted by the scientific community as replacements, reductions, or refinements to animal tests including recommendations and test methods of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM; http://iccvam.niehs.nih.gov/home.htm) approved by the Commission. 77 FR 38751. The proposed codification at 16 CFR 1500.232 would make the ICCVAM recommendations and the Commission's animal testing policy more accessible and transparent to interested parties. The Commission has also established a Web page on the CPSC's website at http://www.cpsc.gov/library/animaltesting.html regarding the ICCVAM recommendations and new developments in test methods that avoid or further reduce or refine animal testing. The final statement on the CPSC's animal testing policy is published elsewhere in this *Federal Register*.

B. Response to Comments on the Proposed Rule

In the *Federal Register* of June 29, 2012, we published a proposed rule on revisions to the animal testing regulations (77 FR 38754). We received three comments

on the proposed rule. Two of the comments were from individuals and the third comment was submitted jointly by the Alternatives Research and Development Foundation, American Anti-Vivisection Society, Humane Society of the United States, People for the Ethical Treatment of Animals, and the Physicians Committee for Responsible Medicine.

1. Non-animal Testing Alternatives

Comment: All three commenters urge the Commission to more strongly consider non-animal testing alternatives. One commenter suggests that the NPR underemphasizes *in vitro* and *in silico* alternatives to animal testing throughout relevant sections of 16 CFR part 1500. The commenter gives examples of *in vitro* tests to support this assertion.

Response: The Commission agrees that *in vitro* and *in silico* tests should be mentioned in the regulation as general options in a testing strategy and the rule has been revised accordingly.

2. Alternatives

Comment: One commenter notes that the Commission's stated preference for human data/experience over animal testing results is not referenced in the relevant sections of 16 CFR part 1500. The commenter also provides a number of examples where *in vivo* test methods were detailed while the preference for alternatives was mentioned only briefly.

Response: The FHSA direct that reliable human experience data take precedence over differing results from animal tests. 15 U.S.C. 1261(h)(2). Therefore, the Commission would always consider human experience with products and substances first, when it exists, followed by a thorough examination of the existing animal database.

The Commission likewise recommends this approach to manufacturers who are labeling substances to indicate a hazard. Accordingly, the proposed rule has been revised to make the preference for human data clearer in the regulatory text.

3. *In vivo* testing

Comment: One commenter suggests that the regulations uncouple definitions of toxic effects from specific animal test results and that these animal tests are "enumerated with such detail as part of the definition [as to be] problematic." The commenter urges the Commission to remove nearly all references to the *in vivo* tests that comprise the existing text of 16 CFR 1500.3(c)(1–4), 1500.40, 1500.41, and 1500.42.

Response: The Commission disagrees that the hazard definitions using animal test methods are problematic. The test methods currently described in the FHSA and relevant sections of 16 CFR part 1500 are intended to show how the Commission would make a hazard determination in the absence of human experiential data, existing animal data, or another acceptable alternative, and are not mandatory or even necessarily recommended test methods for manufacturers. These methods set a baseline standard for hazard testing against which alternative tests can be compared for validity and reliability. They serve as the baseline because they have been used traditionally in hazard testing, not because they are considered superior to other methods. Therefore, while we understand the need to be clear on the discretionary nature of *in vivo* testing, these methods cannot be removed from the regulations altogether. However, the proposed rule has been revised to emphasize the use of *in vitro* and other alternative test methods and prior human experience throughout the relevant sections of 16 CFR part 1500.

Other Comments

Comment: One commenter states that CPSC's animal testing guidelines website should not be limited to listing ICCVAM test methods, but should include new methods than can replace animal-based tests. In addition, this commenter requests that the website contain a process that would allow the public to propose changes to the test methods on the website.

Response: We address these comments in further detail in response to the comments on the Final Statement on Animal Testing Policy published elsewhere in this *Federal Register*. In that policy statement we indicate that alternative test methods beyond those reviewed and recommended by ICCVAM may be acceptable. If a manufacturer or other entity performs a hazard test for FHSA labeling purposes that has not been previously approved by the Commission (*i.e.* an ICCVAM-recommended test method or one of the tests described in the current FHSA), the CPSC staff will review such data on a case-by-case basis before it will post any changes on the animal testing policy website. Although the Commission welcomes input from the public regarding new test methods, proposed changes to the test methods will be posted on the animal testing guidelines Web page only after review of the data regarding the proposed test method by CPSC staff.

C**. Revisions to Animal Testing Regulations**

1. *Definition of highly toxic*. Currently, the test methods in section 1500.3(c)(1)(ii) A–C, used in the definitions of oral, inhalation, and dermal toxicity, respectively, each describe a method for defining a substance as *highly toxic.* The definition of highly toxic in the regulation is:

> (i) A substance determined by the Commission to be highly toxic on the basis of human experience; and/or (ii) A substance that produces death within 14 days in

> half or more than half of a group of: (A) White rats (each weighing between 200 and 300 grams) when a single dose of 50 milligrams or less per kilogram of body weight is administered orally; (B) White rats (each weighing between 200 and 300 grams) when a concentration of 200 parts per million by volume or less of gas or vapor, or 2 milligrams per liter by volume or less of mist or dust, is inhaled continuously for 1 hour or less, if such concentration is likely to be encountered by man when the substance is used in any reasonably foreseeable manner; and/or (C) Rabbits (each weighing between 2.3 and 3.0 kilograms) when a dosage of 200 milligrams or less per kilogram of body weight is administered by continuous contact with the bare skin for 24 hours or less by the method described in §1500.40. The number of animals tested must be sufficient to give a statistically significant result and shall be in conformity with good pharmacological practices.

Because there are other Commission-approved test methods that may be used by CPSC staff or the public for toxicity testing and defining a substance as highly toxic, as reflected in the ICCVAM recommendations and outlined in the CPSC's statement of policy on animal testing published elsewhere in this *Federal Register*, the proposed rule added language (in underline) under new section1500.3(c)(1)(iii) as follows: A substance that produces a result of 'highly toxic' in any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule provides additional language (in underline) to section 1500.3(c)(1) as follows:

> To provide flexibility as to the number of animals tested, and to emphasize *in vitro* testing methods, the following is an alternative to the definition of "highly toxic" in section 2(h) of the act (and paragraph (b)(6) of this section).

In addition, the final rule provides additional language (in underline) to section 1500.3(c)(1) (iii) as follows:

> A substance that produces a result of 'highly toxic' in any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising

> all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

2. *Definition of toxic.* Currently, the test methods in section 1500.3(c)(2)(i) A–C, used in the definitions of oral, inhalation, and dermal toxicity, respectively, each describe a method for defining a substance as *toxic*. The definition of toxic in the regulation is:

> (i) any substance that produces death within 14 days in half or more than half of a group of: (A) White rats (each weighing between 200 and 300 grams) when a single dose of 50 milligrams to 5 grams per kilogram of body weight is administered orally. Substances falling in the toxicity range between 500 milligrams and 5 grams per kilogram of body weight will be considered for exemption from some or all of the labeling requirements of the act, under §1500.82, upon a showing that such labeling is not needed because of the physical form of the substances (solid, a thick plastic, emulsion, etc.), the size or closure of the container, human experience with the article, or any other relevant factors; and/or (B) White rats (each weighing between 200 and 300 grams) when a concentration of more than 200 parts per million but not more than 20,000 parts per million by volume of gas or vapor, or more than 2 but not more than 200 milligrams per liter by volume of mist or dust, is inhaled continuously for 1 hour or less, if such concentration is likely to be encountered by man when the substance is used in any reasonably foreseeable manner; and/or (C) Rabbits (each weighing between 2.3 and 3.0 kilograms) when a dosage of more than 200 milligrams but not more than 2 grams per kilogram of body weight is administered by continuous contact with the bare skin for 24 hours by the method described in §1500.40. The number of animals tested must be sufficient to give a statistically significant result and shall be in conformity with good pharmacological practices.

Because there are other Commission-approved test methods that may be used by CPSC staff or the public for toxicity testing and defining a substance as *toxic,* as reflected in the ICCVAM recommendations, and outlined in the CPSC's statement of policy on animal testing, the proposed rule added language (in underline) under new section 1500.3(c)(2)(iii) as follows:

> *Toxic* also applies to any substance that can be labeled as such, based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule provides additional language (in underline) to section 1500.3(c)(2) as follows:

> To give specificity to the definition of "toxic" in section 2(g) of the act (and restated in paragraph (b)(5) of this section), the following supplements that definition. "Toxic" applies to any substance that is "toxic" (but not "highly toxic") on the basis of human experience. The following categories are not intended to be inclusive.

In addition, in the final rule, the Commission is moving the text from proposed section (iii) to section (i) to more accurately reflect that the text applies to the section on acute toxicity, rather than to create a separate section. Accordingly, the last sentence in section 1500.3(c)(2)(i) has been revised (in underline) as follows:

> *Toxic* also applies to any substance that can be labeled as such, based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

3. *Definition of corrosive*. 16 CFR 1500.3(c)(3) currently states that: Corrosive means "a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application. A substance would be considered corrosive to the skin if, when tested on the intact skin of the albino rabbit by the technique described in §1500.41, the structure of the tissue at the site of contact is destroyed or changed irreversibly in 24 hours or less. Other appropriate tests should be applied when contact of the substance with other than skin tissue is being considered."

The proposed rule added the following text (in underline) to section 16 CFR 1500.3(c)(3):

> Corrosive means a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application. A substance would be considered corrosive to the skin <u>if a weight-of-evidence analysis suggests that it is corrosive or if, when tested by the in vivo</u> technique described in §1500.41, the structure of the tissue at the site of contact is destroyed or changed irreversibly in 24 hours or less. Other appropriate tests should be applied when contact of the substance with other than skin tissue is being considered. <u>A substance could also be labeled corrosive based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.</u>

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule provides additional language (in underline) to section 1500.3(c)(3) as follows:

> Corrosive means a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application. A substance would be considered corrosive to the skin if a weight-of-evidence analysis suggests that it is corrosive<u>, or validated *in vitro* test method suggests that it is corrosive,</u> or if, when tested by the *in vivo* technique described in §1500.41, the structure of the tissue at the site of contact is destroyed or changed irreversibly in 24 hours or less. Other appropriate tests should be applied when contact of the substance with other than skin tissue is being considered. A substance could also be labeled corrosive based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232<u>, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.</u>

4. *Definition of irritant, primary irritant, and eye irritant.* Currently, 16 CFR 1500.3(c)(4) provides that the test methods for *irritant, primary irritant,* and *eye irritant* reference 16 CFR 1500.41 and 1500.42, which each describe a specific animal test method and outcome. For example, 16 CFR 1500.41 states that primary irritation to the

skin is measured by a patch-test technique on the abraded and intact skin of the albino rabbit, clipped free of hair. A minimum of six subjects are used in the skin tests. To test for eye irritants, 16 CFR 1500.42 requires the use of six albino rabbits. Such tests require the test material be placed in one eye of each animal, while the other eye remains untreated, to serve as a control to assess the grade of ocular reaction.

The proposed rule added the following language (in underline) to section 1500.3(c)(4):

> The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results in an empirical score of five or more when tested by the method described in 1500.41; and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232. *Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule provides additional language (in underline) to section 1500.3(c)(4) as follows:

> The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results in an empirical score of five or more when tested by the method described in 1500.41; and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising

all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data. *Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

5. *Method of Testing Toxic Substances*

The method of testing toxic substances is set forth under 16 CFR 1500.40. This method details an acute dermal toxicity assay using rabbits. The method is referenced in § 1500.3(c)(1)(ii)(C) and §1500.3(c)(2)(C). The proposed rule added the following text (in underline) to § 1500.40 immediately after the heading titled, "Method of testing toxic substances":

Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* tests are considered. This analysis, when deemed necessary to carry out, should include any of the following: existing human and animal data, *in vitro* data, structure activity relationships, physicochemical properties, and chemical reactivity. When *in vivo* testing is necessary, a sequential testing strategy is recommended to reduce the number of test animals.

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule modifies the language (in underline) to § 1500.40 as follows:

Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis, including any of the following: existing human and animal data, structure activity relationships, physicochemical properties; and chemical reactivity, or validated *in vitro* or *in silico* testing are recommended to evaluate existing information before *in vivo* tests are considered.

If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals.

6. *Method of Testing Primary Irritant Substances*

The method of testing primary irritant substances is set forth under 16 CFR 1500.41. This method details an acute dermal toxicity assay using rabbits. The method is referenced in §§ 1500.3(c)(3) and 1500.3(c)(4). The proposed rule added the following text (in underline) to §1500.41 immediately after the heading titled, "Method of testing primary irritant substances":

> Guidelines for testing the dermal irritation and corrosivity properties of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include all of the following that are available: human and animal data, structure activity relationships, physicochemical properties, and dermal toxicity. When *in vivo* testing is necessary, a sequential testing strategy is recommended to reduce the number of test animals. The method of testing the dermal corrosivity and primary irritation of substances referred to in §§1500.3(c)(3) and (4), respectively, is a patch-test technique on the abraded and intact skin of the albino rabbit, clipped free of hair…

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule modifies the language (in underline) to § 1500.41 as follows:

> Guidelines for testing the dermal irritation and corrosivity properties of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR § 1500.232. A weight-of-evidence analysis or a validated *in vitro* test method is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include all of the following that are available: human and animal data, structure activity relationships, physicochemical properties, and dermal toxicity. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. The method of testing the dermal corrosivity and primary irritation of substances referred to in §§1500.3(c)(3) and (4), respectively, is a patch-test technique on the abraded and intact skin of the albino rabbit, clipped free of hair . . . .

7. *Test for Eye Irritants*

Section 1500.42 of 16 CFR provides a detailed animal test for eye irritation. The method is referenced in §1500.3(c)(4), which defines *irritation*. The proposed rule added the following text (in underline) to § 1500.42 immediately after the heading titled, "Test for eye irritants":

> Guidelines for *in vivo* and *in vitro* testing of ocular irritation of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include any of the following: existing human and animal data on ocular or dermal irritation, structure activity relationships, physicochemical properties, and chemical reactivity. When *in vivo* testing is necessary, a sequential testing strategy is recommended to reduce the number of test animals. Additionally, the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing is recommended.
> (a)(1) In the method of testing the ocular irritation of a substance referred to in §1500.3(c)(4), six albino rabbits are used for each test substance…

In response to comments that request that the rule contain more references to human experience or *in vitro* or *in silico* tests as non-animal testing alternatives, the final rule modifies the language (in underline) to § 1500.42 as follows:

> Guidelines for *in vivo* and *in vitro* testing of ocular irritation of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis or a validated *in vitro* test method is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include any of the following: existing human and animal data on ocular or dermal irritation, structure activity relationships, physicochemical properties, and chemical reactivity. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. Additionally, the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing is recommended.
> (a)(1) In the method of testing the ocular irritation of a substance referred to in § 1500.3(c)(4), six albino rabbits are used for each test substance…

8. *Editorial changes.*

The proposed rule eliminates the reference in §1500.42(c) to the "Illustrated Guide for Grading Eye Irritation by Hazardous Substances," and the accompanying note. The referenced guide is out of print, and photocopies are rare. Accordingly, the proposed rule amended §1500.42(c) to reference guidelines from the U.S. Environmental Protection Agency (EPA) and the Organisation for Economic Co-operation and Development (OECD) as follows:

> To assist testing laboratories and others interested in interpreting ocular irritation test results, the CPSC animal testing policy Web page at http://www.cpsc.gov/library/animaltesting.html will contain the scoring system defined in the U.S. EPA's Test Guideline, OPPTS 870.2400: Acute Eye Irritation[1] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[2]

The only change made to this section was to update the Web page link for the CPSC animal testing guidelines.

C. 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). The Commission's Directorate for Economic Analysis prepared an assessment of the impact of amending the regulations on animal testing. That assessment found that there would be little or no effect on small businesses and other entities because the amendments will not result in product modifications in order to comply, and they will not result in additional testing or recordkeeping burdens.

D. Environmental Considerations

[1] EPA. 1998. Health Effects Test Guidelines, OPPTS 870.2400 Acute Eye Irritation. EPA 712- C-98-195. Washington, DC: U.S. Environmental Protection Agency. (Available: http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/EPA/EPA_870_2400.pdf)

[2] OECD. 2002. OECD Guideline for the Testing of Chemicals 405: Acute Eye Irritation/Corrosion. Paris: Organisation for Economic Co-operation and Development. (Available: http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECDtg405.pdf)

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.

E. Executive Orders

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations. The preemptive effect of regulations such as this proposed rule is stated in section 18 of the FHSA. 15 U.S.C. 1261n.

F. 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.

G. 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. Section1500.3 is amended by revising paragraph (c)(1) and adding new paragraph (c)(1)(iii) , revising paragraph (c)(2) and the last sentence of paragraph (c)(2)(i), and revising paragraphs (c)(3) and (c)(4), to read as follows:

§ 1500.3 Definitions

* * * * *

(c) * * *

(1) To provide flexibility as to the number of animals tested, and to emphasize *in vitro* testing methods, the following is an alternative to the definition of "highly toxic" in section 2(h) of the act (and paragraph (b)(6) of this section); *Highly toxic* means: * * *

(iii) A substance that produces a result of 'highly toxic' in any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

(2) To give specificity to the definition of "toxic" in section 2(g) of the act (and restated in paragraph (b)(5) of this section), the following supplements that definition. "Toxic" applies to any substance that is "toxic" (but not "highly toxic") on the basis of human experience. The following categories are not intended to be inclusive. * * *

(i) *Toxic* also applies to any substance that can be labeled as such, based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data. * * *

(3) Corrosive means a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application. A substance would be considered corrosive to the skin if a weight-of-evidence analysis suggests that it is corrosive, or validated *in vitro* test method suggests that it is corrosive, or if, when tested by the *in vivo* technique described in §1500.41, the structure of the tissue at the site of contact is destroyed or changed irreversibly in 24 hours or less. Other appropriate tests should be applied when contact of the substance with other than skin tissue is being considered. A substance could also be labeled corrosive based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

(4) The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the

skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results in an empirical score of five or more when tested by the method described in 1500.41; and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data. *Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

* * * * *

3. Amend section 1500.40 by revising the introductory text to read as follows:

§ 1500.40 Method of testing toxic substances.

Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR

1500.232. A weight-of-evidence analysis, including any of the following: existing human and animal data, structure activity relationships, physicochemical properties; and chemical reactivity, or validated *in vitro* or *in silico* testing are recommended to evaluate existing information before *in vivo* tests are considered. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. The method of testing the toxic substances referred to in § 1500.3(c)(1)(ii)(C) and (2)(iii) is as follows:

* * * * *

4. In section 1500.41, add five sentences at the start of the introductory text to read as follows:

§ 1500.41 Method of testing primary irritant substances.

Guidelines for testing the dermal irritation and corrosivity properties of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR § 1500.232. A weight-of-evidence analysis or a validated *in vitro* test method is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include all of the following that are available: human and animal data, structure activity relationships, physicochemical properties, and dermal toxicity. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. The method of testing the dermal corrosivity and primary irritation of substances referred to in §§1500.3(c)(3) and (4), respectively, is a patch-test technique on the abraded and intact skin of the albino rabbit, clipped free of hair. * * *

5. Amend section 1500.42 by adding introductory text, revising paragraph (a)(1), and revising paragraph (c) to read as follows:

§ 1500.42 Test for eye irritants.

Guidelines for *in vivo* and *in vitro* testing of ocular irritation of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis or a validated *in vitro* test method is recommended to evaluate existing information before *in vivo* tests are considered. This analysis should include any of the following: existing human and animal data on ocular or dermal irritation, structure activity relationships, physicochemical properties, and chemical reactivity. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. Additionally, the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing is recommended.

(a)(1) In the method of testing the ocular irritation of a substance referred to in §1500.3(c)(4), six albino rabbits are used for each test substance * * *

* * * * *

(c) To assist testing laboratories and others interested in interpreting ocular irritation test results, the CPSC animal testing policy Web page at http://www.cpsc.gov/library/animaltesting.html will contain the scoring system defined in

the U.S. EPA's Test Guideline, OPPTS 870.2400: Acute Eye Irritation[3] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[4]

Dated:_____

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

[3] EPA. 1998. Health Effects Test Guidelines, OPPTS 870.2400 Acute Eye Irritation. EPA 712- C-98-195. Washington, DC: U.S. Environmental Protection Agency. (Available: http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/EPA/EPA_870_2400.pdf)

[4] OECD. 2002. OECD Guideline for the Testing of Chemicals 405: Acute Eye Irritation/Corrosion. Paris: Organisation for Economic Co-operation and Development. (Available: http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECDtg405.pdf)

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

[Docket No. CPSC-2012-0037]

16 CFR Part 1500

Codification of Animal Testing Policy

AGENCY: Consumer Product Safety Commission.

ACTION: Final Statement on Animal Testing Policy

SUMMARY: The Consumer Product Safety Commission (CPSC or Commission) codifies its statement of policy on animal testing that provides guidance for manufacturers of products subject to the Federal Hazardous Substances Act (FHSA) regarding replacement, reduction, and refinement of animal testing methods.

DATES: The codification is effective [**insert date that is 30 days after publication in the Federal Register**].

FOR FURTHER INFORMATION CONTACT: Leslie E. Patton, Ph.D., Project Manager, Office of Hazard Identification and Reduction, U.S. Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7848; lpatton@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

On June 29, 2012, the Commission issued a notice of proposed rulemaking to amend regulations on the CPSC's animal testing methods under 16 CPR part 1500 to clarify alternative test methods that replace, reduce, or refine animal testing. 77 FR 38754. The final rule on the Commission's regulations on animal testing under 16 CFR

part 1500 is published elsewhere in this *Federal Register*. The final rule on revisions to the animal testing regulations is effective 30 days after publication of the rule in the *Federal Register.*

In addition, on June 29, 2012, the Commission also proposed to codify its statement of policy on animal testing to reflect new methods accepted by the scientific community as replacements, reductions, or refinements to animal tests including recommendations of and test methods of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM; http://iccvam.niehs.nih.gov/home.htm). 77 FR 38751. Codification at 16 CFR 1500.232 would make the ICCVAM recommendations and Commission's animal testing policy more accessible and transparent to interested parties. Although the Commission proposed to make the animal testing policy effective on the date of publication in the *Federal Register*, because the animal testing policy references sections of the animal testing regulations in 16 CFR part 1500, we will make the statement of policy effective on the same date, 30 days after publication of the policy in the *Federal Register.* The Commission has also established a Web page on the CPSC's website at http://www.cpsc.gov/library/animaltesting.html regarding the ICCVAM recommendations and new developments in test methods that replace, reduce, or refine animal testing. After consideration of the comments, the Commission codifies its final statement of policy on animal testing.

B. Response to Comments on the Proposed Policy

In the *Federal Register* of June 29, 2012, we published a proposed statement of policy on animal testing (77 FR 38751). We received two comments on the proposed statement. One commenter was an individual and the other comment was submitted

jointly by the Alternatives Research and Development Foundation, American Anti-Vivisection Society, Humane Society of the United States, People for the Ethical Treatment of Animals, and the Physicians Committee for Responsible Medicine. Both commenters support the use of alternative test methods to eliminate or reduce the use of animals.

1. Alternative Test Methods

Comment: One commenter states that alternative test methods approved for testing potentially hazardous substances were too limited as laid out in the Commission's proposal, and requests that the CPSC broaden its recommendations to *in vitro* and *in silico* tests beyond those already approved by the Commission through ICCVAM. Specifically, the commenter recommends adding methods that were already approved by other regulatory bodies, such as the Organisation for Economic Cooperation and Development (OECD) or the European Centre for the Validation of Alternative Methods (ECVAM EURL). The commenter further suggests that § 1500.232(b) should include any "scientifically acceptable" non-animal alternative that is "fit for the purpose," not limited to those expressly approved by the Commission, nor to those that had undergone an official regulatory validation process.

Response: The Commission agrees that alternatives outside of those which ICCVAM has approved may be acceptable for hazard testing. For hazard testing for the purpose of labeling under FHSA, alternative test methods beyond those reviewed and recommended by ICCVAM may be acceptable because ICCVAM's purview is not exhaustive. In addition, data derived from scientifically valid testing methods can be used to make hazard determinations for substances regulated under FHSA, assuming tests

are reliable, reproducible, and accurate. The Commission encourages hazard testing that supports the replacement, reduction, and refinement of animal test methods while simultaneously maintaining a high degree of scientific integrity. Therefore, if a manufacturer or other entity performs a hazard test for FHSA labeling purposes that has not been previously approved by the Commission (*i.e.,* an ICCVAM-recommended test method or one of the tests described in the current version of the FHSA), CPSC staff will consider the data on a case-by-case basis and, upon review, determine whether to post the test method on the animal testing website.

In the final statement of policy, we refer to *in vitro* and *in silico* methods, in general, as alternative test methods that a manufacturer may wish to consider in lieu of animal testing. We also refer generally to methods that have been deemed acceptable by other national or international organizations, but do not refer to them specifically in the regulations on animal testing under 15 CFR 1500.3, 1500.40-42. The CPSC animal testing webpage at http://www.cpsc.gov/library/animaltesting.html is the platform on which the CPSC will list alternative methods.

Comment: One commenter states that the guidance should explicitly state that "when faced with a decision between a non-animal or animal-based approach, the non-animal approach must be taken."

Response: Although the Commission is issuing this guidance in part to encourage non-animal alternatives to testing, it cannot require manufacturers to adhere to its guidelines. As stated in the CPSC Chronic Hazard Guidelines (57 FR 46626, October, 9, 1992), the Commission does not enforce guidelines as mandatory requirements for manufacturers. A manufacturer may follow a different but scientifically supportable

analysis to determine the potential hazard of a substance as reflected in the alternative test methods posted on the CPSC animal testing webpage at http://www.cpsc.gov/library/animaltesting.html.

2. *In vivo* tests

Comment: One commenter requests that all details on *in vivo* testing procedures be deleted from § 1500.232, including the LD50/LC50 assays at 1500.232(b)(1)(a), the method of testing dermally toxic substances at 1500.232(b)(1)(b), and the ocular irritation assay at 1500.232(b)(1)(c).

Response: The FHSA currently defines acute hazards based on animal test results and identifies irritation and toxicity tests that use animals. Although they are not superior, these *in vivo* test methods remain the baseline to which alternative methods are compared and therefore should remain in the text. Furthermore, the *in vivo* testing described in sections of CFR part 1500 does remain an option to manufacturers performing hazard testing of substances. However, the Commission will emphasize that the use of *in vitro* and other alternative test methods, including a weight-of-evidence approach, and prior human experience are recommended over *in vivo* tests whenever possible throughout the statement of policy. Furthermore, the Commission reiterates its preference for reliable human experience over animal test data. These changes are reflected throughout the summary and statement of policy.

3. Dermal Sensitization Test

Comment: One commenter requests the addition of section 1500.232(b)(1)(d) on alternative test methods for dermal sensitization testing.

Response: The Commission agrees and will add the following section to the statement of animal testing policy:

> Dermal sensitization – An acceptable in vitro test method (examples of valid in vitro tests are identified on the Commission's animal testing website at: http://www.cpsc.gov/library/animaltesting.html), or weight-of-evidence analysis is recommended before in vivo animal sensitization testing is considered to determine appropriate cautionary labeling. The weight-of-evidence analysis should incorporate any existing data on humans and animals, validated *in vitro* or *in silico* test results and any other relevant physicochemical properties that indicate the substance might be a dermal sensitizer. If there is any indication from this analysis that the substance is sensitizing to the skin, the substance should be labeled appropriately.

4. Other Comments

Comment: One commenter requests that we reorder the paragraphs in § 1500.232(a) to ensure that manufacturers first consider the most human-relevant data and methods in determining appropriate labeling

Response: The Commission has already stated a preference for human over animal data throughout the statement of policy, and will maintain the current order of the paragraphs in the animal testing policy.

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.

For the reasons given above, the Commission amends 16 CFR part 1500 as follows:

PART 1500 –[AMENDED]

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

Authority: 15 U.S.C. 1261–1278, 122 Stat. 3016.

2. Add a new section 1500.232 to read as follows:

§ 1500.232 – Statement on Animal Testing Policy

(a) *Summary*.

(1) The U.S. Consumer Product Safety Commission issues this statement of policy on animal testing and alternatives to animal testing of hazardous substances regulated under the Federal Hazardous Substances Act (FHSA). The FHSA requires appropriate cautionary labeling on certain hazardous household products to alert consumers to the potential hazard(s) that the products may present. Among the hazards addressed by the FHSA are toxicity, corrosivity, sensitization, and irritation.

(2) In order to determine the appropriate cautionary labeling, it is necessary to have objective criteria by which the existence of each hazard can be determined. Hazards such as toxicity, tissue corrosiveness, eye irritancy, and skin irritancy result from the biological response of living tissue and organs to the presence of the hazardous substance. One means of characterizing these hazards is to use animal testing as a proxy for the human reaction. In fact, the FHSA defines the hazard category of "highly toxic" in terms of animal toxicity when groups of 10 or more rats are exposed to specified amounts of the substance. 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.

(3) Neither the FHSA nor the Commission's regulations requires animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. If animal testing is conducted, Commission policy supports limiting such tests 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 has prepared this statement of policy with

respect to animal testing to encourage the manufacturers subject to the FHSA to follow a similar policy.

(4) In making the appropriate hazard determinations, manufacturers of products subject to the FHSA should use existing alternatives to animal testing whenever possible. These include: prior human experience (*e.g.,* published case studies), *in vitro* or *in silico* test methods that have been approved by the Commission, literature sources containing the results of prior animal testing or limited human tests (*e.g.,* clinical trials, dermal patch testing), and expert opinion (e.g. hazard assessment, structure-activity analysis). If a manufacturer or other entity performs a hazard test for FHSA labeling purposes that has not been previously approved by the Commission, CPSC staff will consider the data on a case-by-case basis and, upon review, determine whether to post the test method on the animal testing website. The Commission recommends resorting to animal testing only when the other information sources have been exhausted. At this time, the Commission recommends use of the most humane procedures with the fewest animals possible to achieve reliable results. Recommended procedures are summarized in the following statement and can be accessed on the Commission's Webpage at: http://www.cpsc.gov/library/animaltesting.html. If a manufacturer or other entity performs a hazard test for FHSA labeling purposes that has not been previously approved by the Commission (*i.e.,* an ICCVAM-recommended test method or one of the tests described in the current version of the FHSA), CPSC staff will consider the data on a case-by-case basis and, upon review, determine whether to post the test method on the animal testing website.

(b) *Statement of policy on animal testing.*

(1) Neither the FHSA nor the Commission's regulations requires animal testing. Reliable human experience always takes precedence over results from animal data. In the cases where animal tests are conducted, the Commission prefers test methods that reduce stress and suffering in test animals and that use fewer animals while maintaining scientific integrity. To this end, the Commission reviews recommendations on alternative test methods developed by the scientific and regulatory communities. Current descriptions of test method recommendations approved by or known to the Commission can be accessed via the Internet at: http://www.cpsc.gov/library/animaltesting.html. The Commission strongly supports the use of scientifically sound alternatives to animal testing. The following parts of this section outline some of these alternatives. Testing laboratories and other interested persons requiring assistance interpreting the results obtained when a substance is tested in accordance with the methods described here, or in following the testing strategies outlined in the section, should refer to the Commission's animal testing Web page at: http://www.cpsc.gov/library/animaltesting.html.

(a) *Acute toxicity*. The traditional FHSA animal test for acute toxicity determines the median lethal dose (LD50) or lethal concentration (LC50), the dose or concentration that is expected to kill half the test animals. Procedures for determining the median LD50 /LC50 are described in section 2(h)(1) of the Act and supplemented in § 1500.3(c)(1) and (2) and the test method outlined in § 1500.40. The Commission recommends *in vitro* alternatives over *in vivo* LD50/LC50 tests, or using modifications of the traditional LD50/LC50 test during toxicity testing that reduce the number of animals tested whenever possible. Data from *in vitro* or *in silico* test methods that have not been

approved by the Commission may be submitted to the Commission for consideration of their acceptability. Commission-approved testing alternatives are identified on the website at: http://www.cpsc.gov/library/animaltesting.html and include:

(i) *In vitro* and *in vivo* test methods that have been scientifically validated and approved for use in toxicity testing by the Commission;

(ii) Valid *in vitro* methods to estimate a starting dose for an acute *in vivo* test;

(iii) A sequential version of the traditional LD50 /LC50 tests described in § 1500.3(c)(1) and (2) and the test method described in § 1500.40, in which dose groups are run successively rather than simultaneously;

(iv) A limit-dose test where the LD50/LC50 is determined as a point estimate, which can still be used to categorize a hazard, although it gives no information on hazard dose-response. In the limit test, animals (10 rats) each receive a single dose of product at 5g per kilogram of body weight. If not more than one animal dies in 14 days, the product is considered to have an LD50 of greater than 5g/kg, and thus, deemed to be nontoxic. Only if two or more animals die is a second group of 10 rats tested (at a lower dose). This procedure reduces the number of animals tested from the 80 to 100 animals involved in a full LD50 test to, typically, 10 to 20 rats per product. This reduction in the number of animals tested is justified because an exact LD50 is not required by either the FHSA or the regulations. The FHSA requires only a categorical determination that the toxicity is greater than 5g/kg, between 50 mg/kg and 5g/kg, or less than 50 mg/kg.

(b) *Dermal irritation/corrosivity.* An acceptable *in vitro* test method or weight-of-evidence analysis is recommended before *in vivo* dermal irritation testing is considered to

determine appropriate cautionary labeling. The weight-of-evidence analysis should incorporate any existing data on humans and animals, validated *in vitro* or *in silico* test results (valid tests are identified on the Commission's animal testing website at: http://www.cpsc.gov/library/animaltesting.html), the substance's dermal toxicity, evidence of corrosivity/irritation of one or more structurally related substances or mixtures of such substances, data demonstrating low or high pH (≤ 2 or ≥ 11.5) of the substance, and any other relevant physicochemical properties that indicate the substance might be a dermal corrosive or irritant. If there is any indication from this analysis that the substance is either corrosive or irritating to the skin, the substance should be labeled appropriately. If the substance is not corrosive *in vitro*, but no data exist regarding its irritation potential, human patch testing should be considered. If *in vitro* data are unavailable, human patch testing is not an option, and there are insufficient data to determine the weight-of-evidence, a tiered *in vivo* animal test is recommended.

(i) In a tiered in vivo dermal study, a single rabbit is tested initially. If the outcome is positive for corrosivity, testing is stopped, and the substance is labeled appropriately. If the substance is not corrosive, two more rabbits should be patch-tested to complete the assessment of skin irritation potential.

(ii) If a tiered test is not feasible, the Commission recommends the test method described in § 1500.41. Note that in any in vivo dermal irritation test method, the Commission recommends using a semiocclusive patch to cover the animal's test site and eliminating the use of stocks for restraint during the exposure period, thereby allowing the animal free mobility and access to food and water.

(c) *Ocular irritation.* A weight-of-evidence analysis is recommended to evaluate existing information before any *in vivo* ocular irritation testing is considered. This analysis should incorporate any existing data on humans and animals, validated *in vitro* or *in silico* test data (identified on the Commission's animal testing website at: http://www.cpsc.gov/library/animaltesting.html), the substance's dermal corrosivity/irritation (primary skin irritants and corrosives are also usually eye irritants and therefore do not need to be tested in the eye), evidence of ocular irritation of one or more structurally related substances or mixtures of such substances, data demonstrating high acidity or alkalinity of the substance, and any other relevant physicochemical properties that indicate the substance might be a dermal corrosive or irritant or ocular irritant.

(i) When the weight-of-evidence is insufficient to determine a substance's ocular irritation, a Commission-approved *in vitro* or *in silico* assay for ocular irritancy should be run to assess eye irritation potential and determine labeling. Examples of Commission-validated *in vitro* assays are identified on the Commission's animal testing website at: http://www.cpsc.gov/library/animaltesting.html). If no valid *in vitro* test exists, the test strategy for determining dermal corrosion/irritation outlined in section (b)(ii) above can be followed to determine ocular irritation.

(ii) If the dermal test strategy outlined in section (b)(ii) leads to a conclusion of not corrosive, a tiered *in vivo* ocular irritation test should be performed, in which a single rabbit is exposed to the substance initially. If the outcome of this initial test is positive, testing is stopped, and the substance is labeled an eye irritant. If the

outcome of this initial test is negative, one to two more rabbits are tested for ocular irritation, and the outcome of this test will determine the label. If a tiered test is not feasible, the Commission recommends the test method described in § 1500.42.

(iii) When any ocular irritancy testing on animals is conducted, including the method described in § 1500.42, the Commission recommends a threefold plan to reduce animal suffering: (1) the use of preemptive pain management, including topical anesthetics and systemic analgesics that eliminate or reduce suffering that may occur as a result of the application process or from the test substance itself (an example of a typical preemptive pain treatment is two applications of tetracaine ophthalmic anesthetic, 10–15 minutes apart, prior to instilling the test material to the eye); (2) post-treatment with systemic analgesics for pain relief; and (3) implementation of humane endpoints, including scheduled observations, monitoring, and recording of clinical signs of distress and pain, and recording the nature, severity, and progression of eye injuries. The specific techniques that have been approved by the Commission can be found at: http://www.cpsc.gov/library/animaltesting.html.

(d) *Dermal sensitization*. An acceptable *in vitro* test method (examples of valid *in vitro* tests are identified on the Commission's animal testing website at: http://www.cpsc.gov/library/animaltesting.html), or weight-of-evidence analysis is recommended before *in vivo* animal sensitization testing is considered to determine appropriate cautionary labeling. The weight-of-evidence analysis should incorporate any existing data on humans and animals, validated *in vitro* or *in silico* test results, and any

relevant physicochemical properties that indicate the substance might be a dermal sensitizer. If there is any indication from this analysis that the substance is sensitizing to the skin, the substance should be labeled appropriately.

Dated: _____

_____
Todd A. Stevenson, Secretary
Consumer Product Safety Commission