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

Briefing Package:

Final Rule to Revise Animal Testing Sections of 16 CFR Part 1500

and

Codification of an Updated CPSC Policy on Animal Testing

EXECUTIVE SUMMARY

On June 29, 2012, the U.S. Consumer Product Safety Commission (CPSC, Commission) proposed to revise its regulations that have provisions covering animal testing in sections of 16 CFR part 1500 (Federal Register (FR) Volume 77, Number 126). At the same time, the Commission proposed to codify an updated agency policy on animal testing. Staff received three comments on the former proposal (CPSC Docket No. CPSC-2012-0036) and two comments on the latter (CPSC-2012-0037). None opposed the proposed rule or the proposed codification of the policy statement.

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, including toxicity, irritation, and sensitization. Recent innovations in hazard testing by the scientific community focus on the reduction or replacement of animals in testing and the refinement of techniques that alleviate or minimize pain, distress, and/or suffering to animals, while maintaining scientific quality and protecting public health.

The revisions to the FHSA regulations and codification of the statement of policy are not expected to have a significant impact on a substantial number of small businesses or have environmental effects. No comments were received from small businesses on these proposals.

CPSC staff believes that amending the CPSC's regulations on animal testing and codifying an updated policy on animal testing that provides for the use of new technologies and advances in science is important because many people outside the agency, including other federal and international regulatory bodies, are unaware of, or misunderstand, the CPSC's current policy on the use of animals in toxicity testing. Therefore, CPSC staff recommends modifying the relevant sections of 16 CFR part 1500, and codifying its guidance on animal testing under 16 CFR part 232 and in an agency Web page, in order to set forth clear explanations of the agency's animal testing policy.

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

This document has been electronically approved and signed.

November 19, 2012

Memorandum

TO: The Commission
Todd A. Stevenson, Secretary

THROUGH: Mary T. Boyle, Acting General Counsel
Kenneth R. Hinson, Executive Director
Robert J. Howell, Deputy Executive Director for Safety Operations

FROM : J. DeWane Ray, Assistant Executive Director,
Office of Hazard Identification and Reduction
Leslie E. Patton, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT: Revision of Animal Testing Sections of 16 CFR Part 1500 and Codification of Animal Testing Policy

I. BACKGROUND

On June 29, 2012, the U.S. Consumer Product Safety Commission (CPSC, Commission) proposed to revise regulations that refer to animal testing in sections of 16 CFR part 1500 (TAB A). The Commission also proposed to codify an updated agency policy on animal testing (TAB A). Detailed information concerning these issues was provided to the Commission in a briefing package in June 2012.[1]

II. PUBLIC COMMENTS

The Commission requested comments on the notice of proposed rulemaking (NPR) on Revisions to Animal Testing Regulations, 16 CFR part 1500 (CPSC Docket No. CPSC-2012-0036), and the Codification of Animal Testing Policy, Proposed Statement of Policy, 16 CFR Part 1500 (CPSC Docket No. CPSC-2012-0037). The Commission received three comments on the NPR and two comments on the policy codification (TAB B). Changes made to the NPR and proposed animal testing policy based on these comments can be found at TAB C.

A. Public Comments on the NPR

Comments on the NPR were received from two individuals and from an amalgamation of advocacy groups comprised of the Alternatives Research and Development Foundation, American Anti-Vivisection Society, Humane Society of the United States, People for the Ethical

[1] Patton, Leslie. 2012. Memorandum: Revision of Animal Testing Sections of 16 CFR Part 1500 and Proposed Codification of Animal Testing Policy.

Treatment of Animals, and the Physicians Committee for Responsible Medicine. The comments, in their entirety, can be found in TAB B of this briefing package.

All three commenters urge the Commission to consider more strongly non-animal testing alternatives. One commenter states 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. Staff agrees that *in vitro* and *in silico* tests can be mentioned in the regulation as general options in a testing strategy, and the staff's draft final rule revises the proposed rule accordingly.

A commenter notes that the Commission's stated preference for human data/experience over animal testing results is not referenced throughout the relevant sections of 16 CFR part 1500. The commenter also provides a number of examples where *in vivo* test methods were detailed in the proposed rule, while the preference for alternatives was mentioned only briefly. The FHSA directs that reliable human experience data take precedence over differing results from animal tests; therefore CPSC staff would always consider human experience with products and substances first, when it exists, followed by a thorough examination of the existing animal database. Staff likewise recommends this approach to manufacturers who are labeling substances to indicate a hazard. Staff makes this preference for human data clearer in the text of the draft final rule revising 16 CFR part 1500.

A 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. Staff attests that 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. Staff believes that these methods set a baseline approach for hazard testing, against which alternative tests can be compared for reference, 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. At the same time, staff agrees that the use of *in vitro* and other alternative test methods and prior human experience could be emphasized throughout the relevant sections of 16 CFR part 1500. Similarly, the 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." Staff disagrees that hazard definitions using animal test results are problematic because, as just stated, these results are one way to define hazards and therefore have a place in the regulatory definition as do alternative test results.

One commenter states that CPSC's animal testing guidelines website should not be limited to listing test methods of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), but should encompass 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. These comments are addressed in further detail in the staff's response to comments on the final statement on animal testing policy,

which can be found in the next section of this memorandum. CPSC staff agrees that, for hazard testing for the purpose of labeling under the FHSA, alternative test methods beyond those reviewed and recommended by ICCVAM may be acceptable because ICCVAM's purview is not exhaustive. CPSC staff 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, which has not been previously approved by the Commission (*i.e*., it is not an ICCVAM-recommended test method or one of the tests described in the current FHSA), CPSC staff will consider these new data on a case-by-case basis upon review. While CPSC staff welcomes input from the public to its Web page and its animal testing policy, in general, suggestions on proposed changes to the test methods should be made directly to the CPSC via the telephone number or email address provided on the website at: http://www.cpsc.gov/about/contact.html.

B. Public Comments on the Proposed Statement of Policy on Animal Testing

Comments on the proposed statement of policy on animal testing were received from one individual and from the aforementioned amalgamated advocacy group comprised of members of 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. Most comments referred to here are from this group. Comments in their entirety can be found in TAB B of this briefing package.

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. Staff sees no strong reason to reorder the paragraphs, having clearly 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 guidance.

One commenter expresses concern that alternative test methods approved for testing potentially hazardous substances were too limited, as laid out in the Commission's proposal, and they request that staff 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.

CPSC staff agrees that for hazard testing for the purpose of labeling under the FHSA, alternative test methods beyond those reviewed and recommended by ICCVAM may be acceptable because ICCVAM's purview is not exhaustive. Staff further agrees that data derived from scientifically valid testing methods could be used to make hazard determinations for substances regulated

under the FHSA, assuming tests are reliable, reproducible, and accurate. CPSC staff 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.*, if it is not an ICCVAM-recommended test method or one of the tests described in the current FHSA), CPSC staff will consider these data on a case-by-case basis. Staff will add text to the website and guidelines to indicate this policy.

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 approved methods.

A commenter requests that the Commission, "when faced with a decision between a non-animal or animal-based approach, (take) the non-animal approach ..." Although the staff recommends that the Commission issue the draft policy statement, in part to encourage non-animal alternatives to testing, the Commission cannot require manufacturers to adhere to its guidelines. As stated in the CPSC's Chronic Hazard Guidelines (57 FR 46626 1992-10-09), 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.

One commenter wants to see all details on *in vivo* testing procedures deleted from §1500.232, including the LD_{50}/LC_{50} 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). Traditionally, the FHSA has defined acute hazards based on animal test results and called for 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, staff believes they should remain in the CFR. Furthermore, the *in vivo* testing described in sections of CFR part 1500 remains an option to manufacturers performing hazard testing of substances. At the same time, staff agrees that the use of *in vitro* and other alternative test methods, a weight-of-evidence approach, and prior human experience could be emphasized throughout §1500.232. Furthermore, in the draft final policy statement staff includes more explicit language on the Commission's preference for reliable human experience over animal test data.

A commenter suggests we add a § 1500.232(b)(1)(d) on alternative test methods for dermal sensitization testing. CPSC staff agrees to this addition.

III. REGULATORY IMPACT ANALYSIS

In the memorandum prepared for the NPR, the Directorate for Economic Analysis determined that the amendments to the *Hazardous Substances and Articles; Administration and Enforcement*

Regulations (16 CFR part 1500) recommended by CPSC staff are not expected to result in benefits from reductions in the number of injuries or deaths, nor are they anticipated to increase costs to manufacturers (TAB D). Conclusions drawn from the regulatory analysis of the proposed rule have not changed since that time. Similarly, the original analysis of the environmental impact of the proposed rule, which concluded no adverse environmental consequences of the rule, has not changed with the finalization.

IV. COMMISSION OPTIONS

The following options are available for Commission consideration.

With respect to the FHSA regulations:

1. The Commission may vote to issue a rule finalizing changes, as stated in the staff draft final rule, to the regulations at 16 CFR part 1500.

2. The Commission may decline to issue a rule.

With respect to the codification of the animal testing guidelines:

1. The Commission may vote to codify the animal testing guidelines as recommended in the staff's draft Statement of Policy on Animal Testing, 2012.

2. The Commission may decline to codify these guidelines.

V. STAFF RECOMMENDATIONS

The FHSA requires that a product be labeled to reflect the hazards it presents. It does not require animal testing. The Commission policy, whenever possible, is to evaluate product hazards by using alternatives to animal testing. Staff recommends that the Commission vote to finalize the proposed rule, along with the changes made to it by staff, based on public comments.

In addition, staff recommends that the Commission vote to codify an updated policy on animal testing at 16 CFR §1500.32 that provides for the use of new technologies and advances, as well as existing methods. Updating this policy will clarify the agency's animal testing policy and will describe recent innovations in hazard testing by the scientific community. Those innovations t focus on the reduction and replacement of animals in testing, as well as the refinement of techniques that alleviate or minimize pain, distress, and/or suffering to animals, while maintaining scientific quality and protecting public health.

TAB A: FEDERAL REGISTER NOTICE

transportation, is being kept as a pet in a family household in the United States and any dog or cat which, at the time of transportation, is shipped as part of a commercial shipment on a scheduled passenger flight, including shipments by trainers and breeders.

§ 235.2 Applicability.

This part applies to the scheduled domestic and international passenger service of any U.S. air carrier that operates such service with at least one aircraft having a designed seating capacity of more than 60 passenger seats.

§ 235.3 Reports by air carriers on incidents involving animals during air transport.

(a) Each covered carrier shall, within 15 days after the end of the month to which the information applies, submit to the United States Department of Transportation's Aviation Consumer Protection Division a report on any incidents involving the loss, injury, or death of an animal during air transport provided by the air carrier, including incidents on flights by that carrier that are operated with aircraft having 60 or fewer seats. The report shall be made in the form and manner set forth in reporting directives issued by the Deputy General Counsel for the U.S. Department of Transportation and shall contain the following information:

(1) Carrier and flight number;

(2) Date and time of the incident;

(3) Description of the animal, including name, if applicable;

(4) Name and contact information of the owner(s), guardian and/or shipper of the animal;

(5) Narrative description of the incident;

(6) Narrative description of the cause of the incident;

(7) Narrative description of any corrective action taken in response to the incident; and

(8) Name, title, address, and telephone number of the individual filing the report on behalf of the air carrier.

(b) Within 15 days after the end of December of each year, each covered carrier shall submit the following information (this information may be included in any report that the carrier may file for the loss, injury, or death of animals during the month of December):

(1) The total number of incidents involving an animal during air transport provided by the air carrier for the entire calendar year, including incidents on flights by that carrier that are operated with aircraft having 60 or fewer seats. The report shall include subtotals for loss, injury, and death of animals. Report "0" for any category for which there were no such incidents. If the carrier had no reportable incidents for that calendar year, it shall report "0" in each category.

(2) The December report must contain the following certification signed by your authorized representative: "I, the undersigned, do certify that this report has been prepared under my direction in accordance with the regulations in 14 CFR Part 235. I affirm that, to the best of my knowledge and belief, this is a true, correct and complete report."

[FR Doc. 2012–15824 Filed 6–28–12; 8:45 am]

BILLING CODE 4910–9X–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: Proposed Statement of Policy on Animal Testing

SUMMARY: The Consumer Product Safety Commission (CPSC or Commission) proposes to codify its statement of policy on animal testing, as amended, which was previously published in the Federal Register. The amended statement of policy on animal testing is intended for manufacturers of products subject to the Federal Hazardous Substances Act (FHSA) to find alternatives to animal testing and reduce the number of animal tests under the FHSA.

DATES: Written comments and submissions in response to this notice must be received by September 12, 2012.

ADDRESSES: You may submit comments, identified by Docket No. CPSC–2012–0037, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

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

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

Written Submissions

Submit written submissions in the following way:

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

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

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

FOR FURTHER INFORMATION CONTACT: 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) 504–7849; *lpatton@cpsc.gov.*

SUPPLEMENTARY INFORMATION:

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 test methods related to testing on animals to determine the existence of the hazards addressed by the FHSA.

On May 30, 1984, the Commission adopted an animal testing policy that minimized the number of test animals required for toxicity testing and clarified when animal testing might be needed (1984 Policy) published in the Federal Register on May 30, 1984 (49 FR 22522). These guidelines advised product manufacturers to use alternatives to animal testing whenever possible, including: (1) Prior human experience, (2) existing animal or limited human test results, and (3) expert opinion. The 1984 Policy stated:

It is important to keep in mind that neither the FHSA nor the Commission's regulations require any firm to perform animal tests. The statute and its implementing regulations only require that a product be labeled to reflect the

hazards associated with that product. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to the lowest feasible number and taking every feasible step to eliminate or reduce the pain or discomfort that can be associated with such tests* * *. The Commission resorts to animal testing only when the other information sources have been exhausted. Furthermore, the FHSA regulations, at 16 CFR 1500.4, clearly state that reliable human experience shall take precedence over different results from animal data.

Id. at 22523. The 1994 Policy also stated that if non-animal test systems for prediction of toxicity and irritancy are accepted by the scientific community as adjuncts or alternatives to whole-animal testing, "[The CPSC Directorate for] Health Sciences will incorporate the techniques into the Commission's compliance program to the extent feasible and will recommend any changes to the Commission's statutes or regulations that may become appropriate as the result of advances in testing methods that are developed." *Id.*

Since the 1994 Policy, there have been new methods accepted by the scientific community as replacements or adjuncts to animal tests for predictions of toxicity and irritancy. Such developments in testing have been made in recent years, particularly since the National Institutes of Health Revitalization Act was passed in 1993 (Pub. L. 103–43, Section 1301), directing the National Institute of Environmental Health Sciences (NIEHS) to establish a method and criteria for the validation and regulatory acceptance of alternative testing methods. The NIEHS created the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM; *http://iccvam.niehs.nih.gov/home.htm*), which was made permanent by the ICCVAM Authorization Act of 2000, Public Law 106–545. The duties of ICCVAM are to review, optimize, and validate new, revised, or alternative test methods that encourage the reduction, refinement, or replacement of the use of animals in testing. ICCVAM has representatives from 15 federal regulatory and research agencies, including the CPSC. These agencies generate, use, or provide information from toxicity test methods for risk assessment purposes. In addition, ICCVAM provides test recommendations to federal agencies and other stakeholders to facilitate appropriate interagency and international harmonization of toxicological test protocols.

ICCVAM submits recommendations for a test method to federal agencies that require or recommend acute or chronic toxicological testing. According to Public Law 106–545, these agencies should promote and encourage the development and use of alternatives to animal test methods for regulatory purposes, and ensure that any new or revised acute or chronic toxicity test method is valid for its proposed use. Federal agencies have 180 days from the time of submission to identify any relevant test methods for which the ICCVAM test recommendations may be added or substituted, review such test recommendations, and notify ICCVAM if they will adopt the ICCVAM test recommendations. Since 2003, the Commission has approved, where applicable, the recommendations made by ICCVAM to reduce and refine animal testing applicable to test methods under the FHSA. In order to make the ICCVAM recommendations and Commission's animal testing policy more accessible and transparent to interested parties, the Commission proposes to update its regulations on animal testing at 16 C.F.R. part 1500, published elsewhere in this Federal Register, and establish a Web page on the CPSC's Web site at *http://www.cpsc.gov/businfo/animaltesting.html* regarding the ICCVAM recommendations and new developments in test methods that further reduce or refine animal testing.

In addition, the Commission proposes to update its statement on animal testing policy to reflect the ICCVAM recommendations that have been reviewed and adopted by the CPSC as being appropriate tests for assessing hazards under the FHSA. In order to make this statement of policy more accessible and transparent to interested parties, the Commission proposes to codify the policy at 16 CFR 1500.232.

Since this is a statement of policy, a delayed effective date is not required. 5 U.S.C. 553(d)(2). A delayed effective date is not required for the additional reason that this policy is not a substantive rule. 5 U.S.C. 553(d)(3). Accordingly, this codification will become effective upon the publication of a final policy statement 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.

For the reasons given above, the Commission proposes to amend 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; the Consumer Product Safety Improvement Act of 2008, Pub. L. 110–314, § 104, 122 Stat. 3016 (August 14, 2008).

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 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 *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to a minimum number of animals, and the policy also advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. 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, literature sources that record the results of prior animal testing or limited human tests, and expert opinion. 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 Web page at: *http://www.cpsc.gov/businfo/animaltesting.html*.

(b) *Statement of Policy on Animal Testing.*

(1) The Commission reviews staff recommendations on alternative test methods developed by the scientific and regulatory communities. Current descriptions of test method recommendations approved by the Commission can be accessed via the Internet at: *http://www.cpsc.gov/businfo/animaltesting.html*. Overall, the Commission prefers test methods that reduce stress and suffering in test animals and that use none or fewer animals while maintaining scientific integrity. The Commission strongly supports the use of validated 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 this statement of policy and the regulations under 16 CFR part 1500, should refer to the Commission's animal testing Web page at *http://www.cpsc.gov/businfo/animaltesting.html*.

(a) Acute toxicity—The traditional FHSA animal test for acute toxicity determines the median lethal dose (LD_{50}) or lethal concentration (LC_{50}), the dose or concentration that is expected to kill half the test animals. Procedures for determining the median LD_{50}/LC_{50} are described in section 2(h)(1) of the FHSA and supplemented in § 1500.3(c)(1) and (2) and the test method outlined in § 1500.40. The Commission recommends using modifications of the traditional LD_{50}/LC_{50} test during toxicity testing that reduce the number of animals tested, whenever possible. Approved modifications are identified on the Web site at: *http://www.cpsc.gov/businfo/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 LD_{50}/LC_{50} 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 LD_{50}/LC_{50} is determined as a point estimate, which can still be used to categorize a hazard, although it gives no information on hazard dose response.

(b) Dermal irritation/corrosivity—A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* dermal irritation testing is considered to determine appropriate cautionary labeling. This analysis should incorporate any existing data on humans and animals, validated *in vitro* test results (valid tests are identified on the Commission's animal testing Web site at: *http://www.cpsc.gov/businfo/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, and human patch testing is not an option, 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 semi-occlusive 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* test data (identified on the Commission's animal testing Web site at: *http://www.cpsc.gov/businfo/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 that 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* assay for ocular irritancy should be run to assess eye irritation potential and determine labeling. Valid *in vitro* assays are identified at: *http://www.cpsc.gov/businfo/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 considered necessary, 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; (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/businfo/animaltesting.html*.

Dated: June 25, 2012.

Todd A. Stevenson,

Secretary, Consumer Product Safety Commission.

[FR Doc. 2012–15882 Filed 6–28–12; 8:45 am]

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: Notice of Proposed Rulemaking; Revisions to Animal Testing Regulations

AGENCY: Consumer Product Safety Commission.

ACTION: Notice of proposed rulemaking.

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

DATES: Written comments must be received by September 12, 2012.

ADDRESSES: You may submit comments identified by Docket No. CPSC–2012–0036, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

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

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

Written Submissions

Submit written submissions in the following way:

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

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

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

FOR FURTHER INFORMATION CONTACT: 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) 504–7948; *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 test methods related to testing on animals to determine the existence of the hazards addressed by the FHSA.

On May 30, 1984, the Commission adopted an animal testing policy that minimized the number of test animals required for toxicity testing and clarified when animal testing might be needed (1984 Policy) (49 FR 22322). These guidelines advised product manufacturers to use alternatives to animal testing whenever possible, including: (1) Prior human experience, (2) existing animal or limited human test results, and (3) expert opinion. The 1984 Policy stated:

> It is important to keep in mind that neither the FHSA nor the Commission's regulations require any firm to perform animal tests. The statute and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to the lowest feasible number and taking every feasible step to eliminate or reduce the pain or discomfort that can be associated with such tests. * * * The Commission resorts to animal testing only when the other information sources have been exhausted. Furthermore, the FHSA regulations, at 16 CFR 1500.4, clearly state that reliable human experience shall take precedence over different results from animal data.

Id. at 22523. The 1984 Policy also stated that if non-animal test systems for prediction of toxicity and irritancy are accepted by the scientific community as adjuncts or alternatives to whole-animal testing, ''[The CPSC Directorate for] Health Sciences will incorporate the techniques into the Commission's compliance program to the extent feasible and will recommend any changes to the Commission's statutes or regulations that may become appropriate as the result of advances in testing methods that are developed.'' *Id.*

Since the 1984 Policy, there have been new methods accepted by the scientific community as replacements or adjuncts to animal tests for predictions of toxicity and irritancy. Such developments in testing have been made in recent years, particularly since the National Institutes of Health Revitalization Act was passed in 1993 (Pub. L. 103–43, Section 1301), directing the National Institute of Environmental Health Sciences (NIEHS) to establish a method and criteria for the validation and regulatory acceptance of alternative testing methods. The NIEHS created the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM; *http://iccvam.niehs.nih.gov/home.htm*), which was made permanent by the ICCVAM Authorization Act of 2000, Public Law 106–545. The duties of ICCVAM are to review, optimize, and validate new, revised, or alternative test methods that encourage the reduction, refinement, or replacement of the use of animals in testing. ICCVAM has representatives from 15 federal regulatory and research agencies, including the CPSC. These agencies generate, use, or provide information from toxicity test methods for risk assessment purposes. In addition, ICCVAM provides test recommendations to federal agencies and other stakeholders to facilitate appropriate interagency and international harmonization of toxicological test protocols.

ICCVAM submits recommendations for a test method to federal agencies that require or recommend acute or chronic toxicological testing. According to Public Law 106–545, these agencies should promote and encourage the development and use of alternatives to animal test methods for regulatory purposes, and ensure that any new or revised acute or chronic toxicity test method is valid for its proposed use. Federal agencies have 180 days from the

time of submission to identify any relevant test methods for which the ICCVAM test recommendations may be added or substituted, review such test recommendations, and notify ICCVAM if they will adopt the ICCVAM test recommendations. Since 2003, the Commission has approved, where applicable, the recommendations made by ICCVAM to reduce and refine animal testing applicable to test methods under the FHSA. In order to make the ICCVAM recommendations and Commission's animal testing policy more accessible and transparent to interested parties, the Commission proposes to codify its updated animal testing policy at 16 CFR 1500.232, published elsewhere in this Federal Register, and establish a Web page on the CPSC's Web site at *http://www.cpsc.gov/businfo/animaltesting.html* regarding the ICCVAM recommendations and new developments in test methods that further reduce or refine animal testing.

In addition, to reflect more accurately the ICCVAM recommendations and updated test methods approved by the Commission, this proposed rule amends the Commission's regulations that interpret, supplement, or provide alternatives to definitions on animal test methods used to aid in the classification of hazardous substances under the FHSA.

B. Proposed Amendments

All of the proposed amendments to 16 CFR part 1500 clarify or add language to explain that alternative test methods exist that avoid or reduce animal testing, which have been approved by the Commission.

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 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.

The proposed amendment makes clear that the animal tests are not the only means to test or define a product's toxicity under the FHSA, nor are they the only methods used by the CPSC to assess product toxicity. 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 adds language under new 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.*

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 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.

The proposed amendment makes clear that the animal tests are not the only means to test or define a product's toxicity under the FHSA, nor are they the only methods used by the CPSC to assess product toxicity. 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 published elsewhere in this Federal Register, the proposed rule adds language 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.*

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 method of testing described in § 1500.41 is a test for acute dermal toxicity. The proposed rule amends this definition to make explicit that the animal testing is not the only testing method used or accepted by the CPSC, or the preferred method. Accordingly, the proposed rule adds 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 if a weight-of-evidence analysis 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.*

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 clarifies that the method for testing for irritant substances should not be based solely on these specific animal tests because there are other scientifically valid ways of testing for irritants, including methods that do not use animals. Accordingly, the proposed rule adds the following text (in underline) to section 1500.3(c)(4):

The definition of irritant in section 2(j) of the act (restated in paragraph (b)(6) 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.

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). Although the method described in § 1500.40 is one way of assessing a substance's acute dermal toxicity, this method is not mandatory, and it is not the only or preferred method for evaluating dermal toxicity. Accordingly, the proposed rule adds 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.

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). Although the method described in § 1500.41 is one way of assessing a substance's dermal irritation/corrosivity, this method is not mandatory, and it is not the only or preferred method for evaluating a substance's dermal irritation/corrosivity. Accordingly, the proposed rule adds 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 * * *

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*. Although the method described in § 1500.42 is one way of assessing a substance's properties of ocular irritation, this method is not mandatory, and it is not the only or preferred method of assessing a substance's properties of ocular irritation. Accordingly, the proposed rule adds 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 * * *

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. Instead, the proposed rule amends § 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/businfo/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]

[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://ccvam.niehs.nih.gov/SuppDocs/FullDocs/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://ccvam.niehs.nih.gov/SuppDocs/FullDocs/OECD/OECD_gl405.pdf*).

C. Impact on Small Businesses

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

The Commission's Directorate for Economic Analysis prepared a preliminary 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 proposed amendments will not result in product modifications in order to comply, and they will not result in additional testing or recordkeeping burdens. Based on the foregoing assessment, the Commission preliminarily finds that the proposed rule would not have a significant impact on a substantial number of small entities.

D. Environmental Considerations

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

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). We propose that the rule would take effect 30 days after publication of a final rule in the Federal Register.

List of Subjects in 16 CFR Part 1500

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

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

PART 1500—[AMENDED]

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

Authority: 15 U.S.C. 1261–1278, 122 Stat. 3016; the Consumer Product Safety Improvement Act of 2008, Pub. L. 110–314, § 104, 122 Stat. 3016 (August 14, 2008).

2. Amend section 1500.3 by adding new paragraphs (c)(1)(iii) and (c)(2)(iii) and revise paragraphs (c)(3) and (c)(4), to read as follows:

§ 1500.3 Definitions.

* * * * *

(c) * * *

(1) * * *

(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.

(2) * * *

(iii) *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.

(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 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.

(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 the 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.

* * * * *

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 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, physiochemical properties, and chemical reactivity. When *in vivo* testing is necessary, 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 § 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 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, physiochemical 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. * * *

5. Amend section 1500.42 by adding introductory text, adding a sentence at the beginning of 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 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 * * *

* * * * *

(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/businfo/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]

[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://ntp.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: Organization for Economic Co-operation and Development. (Available: *http://ntp.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECDg405.pdf*).

Dated: June 25, 2012.

Todd A. Stevenson,

Secretary, U.S. Consumer Product Safety Commission.

[FR Doc. 2012–15882 Filed 6–28–12; 8:45 am]

BILLING CODE 6355–01–P

DEPARTMENT OF THE TREASURY

Alcohol and Tobacco Tax and Trade Bureau

27 CFR Part 5

[Docket No. TTB–2012–0002; Notice No. 127A; Re: Notice No. 127]

RIN 1513–AB93

Proposed Amendment to the Standards of Identity for Distilled Spirits; Comment Period Extension

AGENCY: Alcohol and Tobacco Tax and Trade Bureau, Treasury.

ACTION: Notice of proposed rulemaking; extension of comment period.

SUMMARY: The Alcohol and Tobacco Tax and Trade Bureau (TTB) is extending the comment period for Notice No. 127, Proposed Amendment to the Standards of Identity for Distilled Spirits, for an additional 10 days. In Notice No. 127, a notice of proposed rulemaking published in the Federal Register on April 30, 2012, TTB proposes to amend the standards of identity regulations for distilled spirits to include "Cachaça" as a type of rum distinctive to Brazil.

DATES: Written comments on Notice No. 127 are now due on or before July 9, 2012.

ADDRESSES: You may send comments on Notice No. 127 to one of the following addresses:

- *http://www.regulations.gov:* To submit comments via the Internet, use the comment form for Notice No. 127 as posted within Docket No. TTB–2012–0002 on "Regulations.gov," the Federal e-rulemaking portal;
- *U.S. Mail:* Director, Regulations and Rulings Division, Alcohol and Tobacco Tax and Trade Bureau, P.O. Box 14412, Washington, DC 20044–4412.
- *Hand Delivery/Courier in Lieu of Mail:* Alcohol and Tobacco Tax and Trade Bureau, 1310 G Street NW., Suite 200–E, Washington, DC 20005.

See the Public Participation section of this notice for specific instructions and requirements for submitting comments, and for information on how to request a public hearing.

You may view copies of all rulemaking documents, supporting materials, and any comments related to this proposal within Docket No. TTB–2012–0002 at *http://www.regulations.gov.* A link to the docket is posted on the TTB Web site at *http://www.ttb.gov/regulations_laws/all_rulemaking.shtml* under Notice No. 127. You also may view copies of all related rulemaking documents, supporting materials, and any comments related to this proposal by appointment at the TTB Information Resource Center, 1310 G Street NW., Washington, DC 20005. Please call 202–453–2270 to make an appointment.

FOR FURTHER INFORMATION CONTACT: Christopher M. Thiemann, Regulations and Rulings Division, Alcohol and Tobacco Tax and Trade Bureau, 1310 G Street NW., Suite 200E, Washington, DC 20005; telephone 202–453–1039, ext. 139.

SUPPLEMENTARY INFORMATION: In Notice No. 127, published in the Federal Register on April 30, 2012, at 77 FR 25382, the Alcohol and Tobacco Tax and Trade Bureau (TTB) proposes to amend its regulations concerning the standards of identity for distilled spirits at 27 CFR 5.22 to include "Cachaça" as a type of rum and as a distinctive product of Brazil. TTB undertook this rulemaking action in response to a petition from the Government of Brazil, and in response to an agreement between the United States and Brazil setting out a procedure that could lead each party to recognize certain distinctive distilled spirits produced in the other party's territory. The agreement provides in part that if, following the publication of a notice of proposed rulemaking, the United States publishes a final rule that lists Cachaça as a type of rum distinctive to Brazil, then Brazil, within 30 days thereafter, will recognize Bourbon Whiskey and Tennessee Whiskey as distinctive products of the United States.

The 60-day comment period for Notice No. 127 originally was set to close on June 29, 2012. On June 15, 2012, TTB received a comment from the European Union requesting an extension of the comment period "in order to have time to analyze and prepare comments" on the proposal (see Comment 4 within Docket No. TTB–2012–0002). In response to this request, TTB is extending the comment period for an additional 10 days, and, therefore, comments on Notice No. 127 are now due on or before July 9, 2012.

Drafting Information

Michael D. Hoover of the Regulations and Rulings Division drafted this notice.

TAB B: PUBLIC COMMENTS

The Commission published a request for comments in the *Federal Register* on two issues: the notice of proposed rulemaking (NPR) on Revisions to Animal Testing Regulations (77 FR 38754) and the Codification of Animal Testing Policy, Proposed Statement of Policy (77 FR 38751). The Commission received three comments on the NPR and two comments on the policy codification. The original comments are reproduced in the following section.

Comments on CPSC Docket No. CPSC-2012-0036: Notice of Proposed Rulemaking (NPR) on Revisions to Animal Testing Regulations, 16 CFR Part 1500

September 12, 2012

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
lpatton@cpsc.gov

Dear Dr. Patton,

The following comments are submitted on behalf of the Alternatives Research & 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 in response to CPSC Docket No. CPSC-2012-0036, announced in the Federal Register on June 29, 2012. The parties to this submission are national animal protection, health, and scientific advocacy organizations with a combined constituency of more than 10 million members who share the common goal of promoting reliable and relevant regulatory testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animals.

General Comments

We agree that the Consumer Product Safety Commission's (CPSC or the Commission) proposal to amend and update its definitions and methods as intended for manufacturers of products subject to the Federal Hazardous Substances Act (FHSA) is important and overdue. We appreciate CPSC's stance that manufacturers should use alternatives to animal testing and reduce the number of animal tests under FHSA. We support the view stated in the 1984 policy that, "The Commission resorts to animal testing only when the other information sources have been exhausted." Furthermore, the FHSA regulations, at 16 CFR 1500.4, clearly state that "reliable human experience shall take precedence over different results from animal data."

Although the revised definitions provide some clarity that data from nonanimal methods are allowed, CPSC regulations maintain an emphasis on animal-data-derived definitions of toxicity that do not fully capture the current spectrum of approaches or leave room for future scientific advances. A more appropriate approach would uncouple definitions of toxic effects from specific animal test results. In 2007, the National Academies recommended nothing short of a complete overhaul in the way chemicals are routinely assessed for potential hazardous effects in its report *Toxicity Testing in the 21st Century: A Vision and a Strategy*. We encourage CPSC to follow this vision and harness

the momentum of "Toxicology in the 21st Century" by moving entirely away from reliance on animal data to define product toxicities.

Additionally, we favor the establishment of the CPSC-proposed web site that would list test methods acceptable to the Commission, however it appears that it will include only "ICCVAM recommendations and new developments in test methods that reduce or refine animal testing." While the web site is a good idea because it will allow for continual update of accessible methods, we suggest that the web site also include new methods that can replace animal-based tests, in keeping with the spirit of the "three Rs," which aim to replace, reduce, and refine the use of animals. Further, we request that the web site contain a process that would allow the public to transparently propose changes to the test methods detailed on the web site, such as a monitored forum or web form.

The following amendments to the definitions proposed by CPSC improve the Commission's policy with respect to reducing the reliance on animal testing. Below we offer specific suggestions that would allow for a more complete application of existing animal reduction approaches and a more expedited uptake of future developments.

Specific Text Suggestions

1. *Definition of Highly Toxic*

While we appreciate that a known toxic substance based on human experience qualifies as a method to determine toxicity, the fact that animal toxicity is enumerated with such detail as part of the definition is problematic. A more holistic definition of toxicity based on human experience and *in vitro* data while utilizing existing animal data, if available, is the more appropriate approach. The proposed additional sentence as point (iii) in italics below simply informs the reader to visit the new portion of 16 CFR 1500 to see a list of approved test methods described in the animal testing policy, despite the fact that the rest of the definition is intrinsically linked to animal toxicity. We suggest the following:

> "(i) A substance determined by the Commission to be highly toxic on the basis of human experience; and/or (ii) A weight-of-evidence analysis, existing human and animal data, *in vitro* data, structure activity relationships, physicochemical properties, and chemical reactivity ~~(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.~~ (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.*"

2. *Definition of Toxic*

After the three *in vivo* methods are described to determine whether a substance is toxic via the oral, inhalation, or dermal routes it is stated in the Federal Register notice that, "The proposed amendment makes clear that the animal tests are not the only means to test or define a product's toxicity under FHSA, nor are they the only methods used by the CPSC to assess product toxicity." However, we find no reference to human experience or *in vitro* methods, both of which can serve as viable alternatives to animal testing. As above, there is only one sentence added to the end of the definition informing the reader to view the animal testing policy stated in 16 CFR 1500. The definition of "toxic," according to the language proposed, is exclusively based on animal toxicity. As explained above, specific description of animal tests should be removed from the regulations. We suggest the following:

"(i) A substance determined by the Commission to be toxic on the basis of human experience; and/or (ii) a weight-of-evidence analysis, existing human and animal data, *in vitro* data, structure activity relationships, physicochemical properties, and chemical reactivity ~~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.~~

(iii) *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."*

3. *Definition of Corrosive*

We support the inclusion of weight-of-evidence analysis in the definition of a corrosive substance. We find it alarming, however, that the proposed amended text maintains a primary definition based on animal test results and there is no explicit mention of *in vitro* approaches. Given the current state of the art, most chemicals can be assessed for corrosivity *in vitro*, and no or extremely rare animal testing should be done for this endpoint. For example, that *in vitro* methods using Reconstructed Human Epidermis (RhE) exist to determine corrosivity as detailed in OECD Test Guideline 431, In Vitro Skin Corrosion: Human Skin Model Test[1]. EpiDerm[2], SkinEthic[3], EpiSkin[4], and CellSystem EST1000[5] are all validated RhE models that can be used to evaluate corrosivity. OECD Test Guideline 435, In Vitro Membrane Barrier Test Method for Skin Corrosion[6] is a physico-chemical test that assesses corrosive potential by measuring the time it takes for a chemical to break through a synthetic macromolecular membrane. For these reasons we amend the following text to read:

"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* or in vitro study *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."*

4. *Definition of Irritant, Primary Irritant, and Eye Irritant*

We are again pleased to see that human experience data is listed. However, again the proposed text includes a primary definition based on animal data and there is no explicit mention of *in vitro* approaches. For most chemicals, dermal irritancy can be evaluated using a completely non-animal approach (as detailed by OECD TG 439 In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method); therefore, and with consideration to the above arguments, we suggest the following revisions. We suggest the following:

"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.*"

5. *Method of Testing Toxic Substances*

We appreciate that CPSC states multiple non animal techniques, however this revision should delete reference to *in vivo* testing methods. We suggest the following:

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

Furthermore, the text below at §1500.40 should be deleted from the regulation and provided elsewhere (e.g. the web site) until suitable alternatives are available and specific procedures can be modified or deleted altogether:

> ~~(a) *Acute dermal toxicity (single exposure).* In the acute exposures, the agent is held in contact with the skin by means of a sleeve for periods varying up to 24 hours. The sleeve, made of rubber dam or other impervious material, is so constructed that the ends are reinforced with additional strips and should fit snugly around the trunk of the animal. The ends of the sleeve are tucked, permitting the central portion to "balloon" and furnish a reservoir for the dose. The reservoir must have sufficient capacity to contain the dose without pressure. In the following table are given the dimensions of sleeves and the approximate body surface exposed to the test substance. The sleeves may vary in size to accommodate smaller or larger subjects. In the testing of unctuous materials that~~

~~adhere readily to the skin, mesh wire screen may be employed instead of the sleeve. The screen is padded and raised approximately 2 centimeters from the exposed skin. In the case of dry powder preparations, the skin and substance are moistened with physiological saline prior to exposure. The sleeve or screen is then slipped over the gauze that holds the dose applied to the skin. In the case of finely divided powders, the measured dose is evenly distributed on cotton gauze which is then secured to the area of exposure.~~

[Table omitted]

~~(b) *Preparation of test animal.* The animals are prepared by clipping the skin of the trunk free of hair. Approximately one half of the animals are further prepared by making epidermal abrasions every 2 or 3 centimeters longitudinally over the area of exposure. The abrasions are sufficiently deep to penetrate the stratum corneum (horny layer of the epidermis) but not to distrub the derma; that is, not to obtain bleeding.~~

~~(c) *Procedures for testing.* The sleeve is slipped onto the animal which is then placed in a comfortable but immobilized position in a multiple animal holder. Selected doses of liquids and solutions are introduced under the sleeve. If there is slight leakage from the sleeve, which may occur during the first few hours of exposure, it is collected and reapplied. Dosage levels are adjusted in subsequent exposures (if necessary) to enable a calculation of a dose that would be fatal to 50 percent of the animals. This can be determined from mortality ratios obtained at various doses employed. At the end of 24 hours the sleeves or screens are removed, the volume of unabsorbed material (if any) is measured, and the skin reactions are noted. The subjects are cleaned by thorough wiping, observed for gross symptoms of poisoning, and then observed for 2 weeks.~~

6. *Method of Testing Primary Irritant Substances*

As mentioned above, five RhE models exist and are currently available for commercial use to assess skin irritation potential: EpiDerm, SkinEthic, CellSystem EST1000, LabCyte EPIMODEL-24[9], and EpiSkin. In-depth information on the development and validation of three of these models, which can be used in OECD Test Guideline 439, In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method[9], are available. Potential use of *in vitro* approaches should be mentioned explicitly and not only referenced in the new section of 16 CFR 1500. Specifically, *in vitro* approaches should be recommended preferentially. Given the current state of the art, most chemicals can be assessed for corrosivity and irritation *in vitro*, and no or extremely rare animal testing should be done for these endpoints.

> *"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 and in vitro methods ~~is~~ are 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~~ If in vivo testing is ~~necessary~~ 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 ..."

Furthermore, the rest of the text at §1500.41 should be deleted:

~~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 abraded and intact skin tests. Introduce under a square patch, such as surgical gauze measuring 1 inch by 1 inch and two single layers thick, 0.5 milliliter (in the case of liquids) or 0.5 gram (in the case of solids and semisolids) of the test substance. Dissolve solids in an appropriate solvent and apply the solution as for liquids. The animals are immobilized with patches secured in place by adhesive tape. The entire trunk of the animal is then wrapped with an impervious material, such as rubberized cloth, for the 24-hour period of exposure. This material aids in maintaining the test patches in position and retards the evaporation of volatile substances. After 24 hours of exposure, the patches are removed and the resulting reactions are evaluated on the basis of the designated values in the following table:~~

[Table omitted]

~~Readings are again made at the end of a total of 72 hours (48 hours after the first reading). An equal number of exposures are made on areas of skin that have been previously abraded. The abrasions are minor incisions through the stratum corneum, but not sufficiently deep to disturb the derma or to produce bleeding. Evaluate the reactions of the abraded skin at 24 hours and 72 hours, as described in this paragraph. Add the values for erythema and eschar formation at 24 hours and at 72 hours for intact skin to the values on abraded skin at 24 hours and at 72 hours (four values). Similarly, add the values for edema formation at 24 hours and at 72 hours for intact and abraded skin (four values). The total of the eight values is divided by four to give the primary irritation score; for example:~~

[Table omitted]

7. *Test for Eye Irritants*

Again, there is no mention of *in vitro* techniques, which can be used to assess the

ocular irritation potential of many consumer products. Examples include the Bovine Corneal Opacity and Permeability assay[10], 3D human tissue constructs[11], the Isolated Chicken Eye assay[12], the Cytosensor Microphysiometer assay[13], the Short Term Exposure assay[14], the Fluorescein Leakage assay[15], and the EpiOcular Model[16].

Due to the plethora of currently available *in vitro* techniques, and the inevitable future advancements in nonanimal technology, animal testing for eye irritation should be rare. Furthermore, should a company choose to test using *in vivo* methods, no more than three rabbits should be used (the current language proposes six). Therefore, we suggest the following:

> "*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~~ If in vivo testing is ~~necessary~~ 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...~~"

Furthermore, the text at §1500.42 should be deleted:

> ~~(a)(1) Six albino rabbits are used for each test substance. Animal facilities for such procedures shall be so designed and maintained as to exclude sawdust, wood chips, or other extraneous materials that might produce eye irritation. Both eyes of each animal in the test group shall be examined before testing, and only those animals without eye defects or irritation shall be used. The animal is held firmly but gently until quiet. The test material is placed in one eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test substance is dropped. The lids are then gently held together for one second and the animal is released. The other eye, remaining untreated, serves as a control. For testing liquids, 0.1 milliliter is used. For solids or pastes, 100 milligrams of the test substance is used, except that for substances in flake, granule, powder, or other particulate form the amount that has a volume of 0.1 milliliter (after compacting as much as possible without crushing or altering the individual particles, such as by tapping the measuring container) shall be used whenever this volume weighs less than 100 milligrams. In such a case, the~~

~~weight of the 0.1 milliliter test dose should be recorded. The eyes are not washed following instillation of test material except as noted below.~~

~~(2) The eyes are examined and the grade of ocular reaction is recorded at 24, 48, and 72 hours. Reading of reactions is facilitated by use of a binocular loupe, hand slit-lamp, or other expert means. After the recording of observations at 24 hours, any or all eyes may be further examined after applying fluorescein. For this optional test, one drop of fluorescein sodium ophthalmic solution U.S.P. or equivalent is dropped directly on the cornea. After flushing out the excess fluorescein with sodium chloride solution U.S.P. or equivalent, injured areas of the cornea appear yellow; this is best visualized in a darkened room under ultraviolet illumination. Any or all eyes may be washed with sodium chloride solution U.S.P. or equivalent after the 24-hour reading.~~

~~(b)(1) An animal shall be considered as exhibiting a positive reaction if the test substance produces at any of the readings ulceration of the cornea (other than a fine stippling), or opacity of the cornea (other than a slight dulling of the normal luster), or inflammation of the iris (other than a slight deepening of the folds (or rugae) or a slight circumcorneal injection of the blood vessels), or if such substance produces in the conjunctivae (excluding the cornea and iris) an obvious swelling with partial eversion of the lids or a diffuse crimson red with individual vessels not easily discernible.~~

~~(2) The test shall be considered positive if four or more of the animals in the test group exhibit a positive reaction. If only one animal exhibits a positive reaction, the test shall be regarded as negative. If two or three animals a positive reaction, the test is repeated using a different group of six animals. The second test shall be considered positive if three or more of the animals exhibit a positive reaction. If only one or two animals in the second test exhibit a positive reaction, the test shall be repeated with a different group of six animals. Should a third test be needed, the substance will be regarded as an irritant if any animal exhibits a positive response.~~

~~(c) To assist testing laboratories and other interested persons in interpreting the results obtained when a substance is tested in accordance with the method described in paragraph (a) of this section, an "Illustrated Guide for Grading Eye Irritation by Hazardous Substances" will be sold by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.[1] The guide will contain color plates depicting responses of varying intensity to specific test solutions. The grade of response and the substance used to produce the response will be indicated.~~

~~* * * * *~~

"(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/businfo/ 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]"

We appreciate your consideration of these suggestions. Please direct any questions to the undersigned at abirdie@pcrm.org.

Sincerely,

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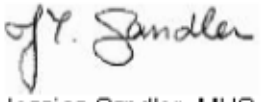

Jessica Sandler, MHS
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People for the Ethical Treatment of Animals

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PUBLIC SUBMISSION

As of: 9/13/12 3:44 PM
Tracking No. 81081b63
Comments Due: September 12, 2012

Docket: CPSC-2012-0036
Hazardous Substances and Articles: Administration and Enforcement Regulations: Notice of Proposed Rulemaking; Revisions to Animal Testing Regulations
Comment On: CPSC-2012-0036-0001
Hazardous Substances and Articles: Revisions to Animal Testing Regulations
Document: CPSC-2012-0036-0002
Comment from Skyler Roth

Submitter Information
Name: Skyler Roth

General Comment
Dear Sir or Madam:

I commend the CPSC for encouraging alternatives to animal testing of hazardous substances. However, I believe that there are two areas where the proposed rule could be modified, to make clearer the importance of avoiding animal testing whenever possible.

First, the references to the CPSC's new animal testing policy in 1500.3(c)(1)(iii) and 1500.3(c)(2)(iii) are hampered by their vagueness and positioning. They mention the policy, but only refer to its "approved test methods". Since they also come after a long description of animal testing, this might be misinterpreted to suggest that the only alternatives are other animal tests. In contrast, 1500.3(c)(3) is more effective, as it mentions the value of "a weight-of-evidence analysis" prior to in vivo tests (though its reference to the new policy is similarly vague). I recommend that all three paragraphs mention weight-of-evidence analysis, and briefly emphasize the animal testing reduction goals of the new policy by mentioning that the "approved test methods" include non-animal tests.

Second, while the Commission's proposed additions to 1500.40 and 1500.41 are excellent, they are not as strong as the addition to 1500.42, which also includes specific guidelines to "avoid or minimize pain and distress". While tests involving the eyes are likely to be particularly harmful, toxic substances and skin irritants can also cause considerable distress to an animal. The report The Ethics of Research Involving Animals by the Nuffield Council on Bioethics states that toxicity testing can cause "external and internal bleeding," among other serious effects. Whenever possible, the pain of such effects should be alleviated. If the specific recommendations for eye irritants are inappropriate to the other tests, I suggest developing more appropriate recommendations or including general language urging the minimization of pain and distress.

Thank you for the opportunity to comment.

Sincerely,
Skyler Roth

PUBLIC SUBMISSION

As of: 9/13/12 3:45 PM
Tracking No. 81073c8b
Comments Due: September 12, 2012

Docket: CPSC-2012-0036
Hazardous Substances and Articles: Administration and Enforcement Regulations: Notice of Proposed Rulemaking; Revisions to Animal Testing Regulations
Comment On: CPSC-2012-0036-0001
Hazardous Substances and Articles: Revisions to Animal Testing Regulations
Document: CPSC-2012-0036-0003
Comment from Jean Public

Submitter Information
Name: Jean Public
Submitter's Representative: None
Organization: None

General Comment
RABBITS SHOUDL BE TAKEN FROM THE LIST OF ANIMALS THAT ARE USED FOR ANY TESTING. NO MORE RABBITS SHOULD BE USED AT ANY TIME. ALSO THI SCHANGE SHOULD REFLECT THAT THIS AGENCY PREFERS OTHER TEST METHODS THATN ABUSIVE TESTS ON ANIMALS. TESTS ON HUMAN CELLS OR ONPEOPLE ARE PREFERRED. IT IS ALSO CLEAR THAT TESTS TESTS ON ANIMALS ARE DECEPTIVE AND NOT REALLY RELEVANT OR MEANINGFUL IN APPLICATION TO WHAT THE PRODUCT WILL DO TO A PERSON. AGAIN, GET THE RABBITS ENTIRE OUT OF THIS TESTING CYCLE. THIS TEST METHOD STARTED IN MIDIEVEL TIMES 1500 AD. WE HAVE MUCH MORE RELIABLE METHODS OF TESTING TODAY THAN ABUSING AND PAINFULLY INJURING AND KILLING RABBITS. More rabbits are used for research in the U.S. than any other covered species. In 1987, an all-time high of 554,385 rabbits were exploited for research and testing. Over the past two decades, rabbit use has gradually declined, with the latest reports indicating that over 200,000 rabbits are utilized annually.

Rabbits are widely used for experimentation and testing mainly due to practical rather than scientific considerations. They are small and usually docile, easily restrained, cheap to maintain, and breed prodigiously.

Most people associate the use of rabbits in laboratories with toxicity testing for cosmetic, personal, and household products. The best known tests are the Draize eye and skin irritancy tests, which are extremely painful and cruel. While being experimented upon, rabbits are also often locked into full-body restraints to prevent them from touching eye or skin sores. These tests are not very reliable, and increasing attention is being paid to the development of alternatives to replace the use of rabbits for these categories of toxicity testing.

For medical products such as vaccines, drugs, and medical devices, rabbits are used to test pyrogenicity (the ability of the product to induce a fever). Additionally, because of their high rate of reproduction, rabbits are also used to test developmental/embryotoxi [*sic*]

Comments on CPSC Docket No. CPSC-2012-0037: Codification of Animal Testing Policy, Proposed Statement of Policy, 16 CFR Part 1500

September 12, 2012

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
lpatton@cpsc.gov

Dear Dr. Patton,

The following comments are submitted on behalf of the Alternatives Research & 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 in response to the Federal Register notice published on June 29, 2012 (Docket No. CPSC-2012-0037). The parties to this submission are national animal protection, and health and scientific advocacy organizations with a combined constituency of more than 10 million members. We share the common goal of promoting reliable and relevant regulatory testing methods and strategies that protect human health while reducing, and ultimately eliminating, the use of animals.

General Comments

We agree that the Consumer Product Safety Commission's (CPSC or the Commission) proposal to codify its statement on animal testing into a Statement on Animal Testing Policy (Policy) as intended for manufacturers of products subject to the Federal Hazardous Substances Act (FHSA) is important and overdue. We appreciate CPSC's explicit stance that manufacturers should use alternatives to animal testing and aim to minimize the number of animal tests conducted to meet FHSA requirements. We strongly support the view that "the Commission prefers tests methods that reduce stress and suffering in test animals and that use none or fewer animals while maintaining scientific integrity."

We also favor implementation of the CPSC-proposed web site, but are concerned that it apparently will include only "ICCVAM recommendations and new developments in test methods that reduce or refine animal testing." While the web site is necessary to allow for frequent update of available approaches, it should also include new approaches that can *replace* animal-based tests in keeping with the spirit of the "three Rs," which aim to replace, reduce, and refine the use of animals. The proposed revisions retain an excess of language that supports animal-based testing; our comments are intended to align CPSC policy with current trends in toxicology being adopted by other US agencies, as well as internationally, that move away from a list of empirical animal data toward more integrated testing and assessment strategies.[1,2,3]

[1] National Research Council. 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy in 2007. Washington, DC: National Academies Press. Public web site accessed on August 29, 2012 at http://www.nap.edu/catalog.php?record_id=11970.

Specific Text Suggestions to the "Statement on Animal Testing Policy"

Appendix A: Specific Text Suggestions – redlined and Appendix B: Specific Text Suggestions – clean, is below. We offered the latter for easy reference to the changes we proposed. Those changes are based on the following discussion.

At its core, as emphasized in the 1984 policy, the FHSA is intended to protect *human* consumers, and "reliable human experience shall take precedence over different results from animal data." Therefore, we suggest revising the order of the Summary paragraphs (§1500.232(a)) to ensure that manufacturers first consider the most human-relevant data and methods for determining cautionary labeling. Specifically, the sentiment captured in paragraph (4), that "manufacturers…should use…prior human experience, literature sources, and expert opinion…" should be discussed first, followed by the key fact that begins paragraph (3), that "Neither the FHSA nor the Commission's regulations require animal testing…"

Inexplicably, *in vitro* or *in silico* toxicology test methods are not mentioned at all. Since it is not likely that this policy will be amended again soon, the text should be written to encompass the direction in which toxicology testing is headed, which is entirely nonanimal, particularly for consumer products.

The revised Policy (§1500.232(a)(3)) states, "animal testing may be necessary in some cases." The Commission must ensure that all nonanimal test methods and strategies have been explored before an animal test is conducted. In practice, manufacturers should understand that, when faced with a decision between a nonanimal or animal-based approach, the nonanimal approach must be taken. Therefore, we recommend an explicit statement to that effect, located in a more prominent place in the revised Policy, as shown in Appendix A and B.

We support the 1984 language from 16 CFR 1500.4 that states "reliable human experience shall take precedence over different results from animal data" as it reinforces the position that human-based information is more relevant to humans scientifically than animal data, and we urge the CPSC to include this language in the amendment.

We are aware that the Commission and FHSA regulations do not specifically require animal testing—or any specific test. Therefore, the "Statement of Policy on Animal Testing" (§1500.232(b)) should make it clear that, while test method recommendations will be available on the CPSC web site, other nonanimal test methods that are not specifically "approved" by the Commission or listed on the web site, as long as they are "scientifically acceptable," (as stated in the 1984 policy) can be used to characterize potential hazards.

Under §1500.232(b), we appreciate that weight-of-evidence approaches and alternatives to, and modifications of, animal tests should be used wherever possible. However, CPSC does not

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[2] Berg N et al. 2011. Toxicology in the 21st century--working our way towards a visionary reality. Toxicol In Vitro. 25(4):874-81.

[3] Stephens ML et al. 2012. Accelerating the development of 21st-century toxicology: outcome of a Human Toxicology Project Consortium workshop. Toxicol Sci. 125(2):327-34.

provide a definition of the term "validated," which the Commission uses repeatedly in this section and throughout the Policy in conjunction with nonanimal test methods. We propose that instead of using the term "validated," the Policy use "scientifically appropriate/acceptable" or "fit for purpose," as "validated" limits the amount of data that could be accepted by CPSC and unduly restricts manufacturers to methods that have undergone extensive regulatory validation. This would be in line with the approach to validation that is being initiated at other regulatory agencies, as a result of the length and expense of traditional regulatory validation, and recognizes that animal tests have never been validated for their (in)ability to predict human outcomes. Finally, the Policy should state that methods 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) are acceptable in replacement, reduction, or refinement strategies of U.S.-based animal testing methods.

In §1500.232(b)(1)(a) (acute toxicity), we suggest that a statement discouraging the conduct of the LD_{50}/LC_{50} test be added. These tests—by definition—poison animals until they die. There is also much scientific consensus that acute poisoning tests are not relevant to human health. The International Council on Harmonization (ICH) removed acute oral toxicity tests from its M3 guidelines for non-clinical safety studies for human clinical trials of pharmaceuticals[4]. Chapman et al. report a consensus among representatives from poison centers, the pharmaceutical and chemical industries, and regulatory bodies that the information the acute test provides is of little value[5]. This is partly because high doses of chemical substances often elicit non-specific effects in animals that have no relevance to incidences of human overdose. In addition, acute toxicity testing typically does not provide information on adverse and functional effects, target organ toxicity, and toxicokinetics that is considered by poison centers to be most useful.

Furthermore, hazard classification, which the acute tests would provide for CPSC review, often does not adequately predict human toxicity. A study of outcomes of human poisoning cases with three organophosphorous pesticides, all categorized as class 2 ($LD_{50} > 5 \leq 50$ mg/kg) by the Globally Harmonized System of Classification and Labelling of Chemicals, found significant differences in severity of symptoms and likelihood of death, despite having similar LD_{50} values from acute toxicity studies[6]. Even in cases for which hazard class has been reported to correlate with mortality, mortality rates are highly variable among substances within a class; in one study, mortality rates for seven compounds in class 1 ranged from 24% to 0%[7].

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[4] ICH. 2009. Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Public web site accessed on August 29, 2012 at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2_Guideline.pdf.

[5] Chapman K *et al*. 2010. The value of acute toxicity studies to support the clinical management of overdose and poisoning: a cross-discipline consensus. *Regul Toxicol Pharmacol*. 58(3):354-9.

[6] Eddleston M *et al*. 2005. Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. *Lancet*. 366: 1452–1459.

[7] Peter JV *et al*. 2010. Is there a relationship between the WHO hazard classification of organophosphate pesticide and outcomes in suicidal human poisoning with commercial organophosphate formulations? *Regul. Toxicol. Pharmacol*. 57: 99–102.

There is strong evidence that *in vitro* assays can be used to classify substance hazards. Recently, the ACuteTox project reported the results of its prevalidation of a tiered testing strategy using eight *in vitro* assays[8]. The outcome of this study reinforced previous results obtained with the 3T3 NRU assay, supporting its use to identify unclassified substances (LD_{50} > 2000 mg/kg) as a first step in a tiered testing strategy. In addition, a number of assays were identified that were able to flag substances as neurotoxicants and nephrotoxicants. These assays could be used to alert on tissue-specific toxicity for substances that are identified as toxic (predicted LD_{50} < 2000 mg/kg) with the 3T3 NRU assay. It was also concluded that the combined use of DEREK and METEOR software is likely to improve the ability to predict the toxicity of an unknown substance or its major metabolites.

Evidence shows that more than 85% of industrial chemicals are non-toxic[9] (Kinsner-Ovaskainen, *et al.*, 2008). Therefore, a weight-of-evidence approach incorporating the 3T3 NRU assay, other in vitro assays, existing information, and QSARS to identify whether a substance is toxic or non-toxic would be an appropriate approach for items under CPSC regulatory purview.

In §1500.232(b)(1)(*b*) (Dermal irritation/corrosivity), the Policy recommends human patch testing or tiered *in vivo* animal testing if a substance is not corrosive *in vitro*. However, this recommendation completely ignores OECD Test Guideline 439, which can detect non-corrosive irritants, and was adopted in 2010[10]. This section must be revised appropriately. Further, regarding §1500.232(b)(1)(*b*)(ii), we wonder under what circumstances a tiered *in vivo* test would be "not feasible." We recommend deleting this sentence.

And again, regarding §1500.232(b)(1)(*c*)(ii), we wonder under what circumstances a tiered *in vivo* eye irritation test would be "not feasible." We recommend deleting this sentence.

Several methods for determination of dermal sensitization have been developed and are currently being evaluated for regulatory use;[11] therefore, the Policy should include section 1500.232(b)(1)(*d*) on dermal sensitization. This section should encourage companies to use these available *in vitro* methods.

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[8] AXLR8 Consortium. 2011. Alternative Testing Strategies Progress Report. Freie Universität Berlin, Institute of Pharmacy, Berlin, Germany. Public web site accessed on August 29, 2012 at http://axlr8.eu/assets/axlr8-progress-report-2011.pdf.

[9] Kinsner-Ovaskainen A *et al.* 2008. ECVAM ongoing activities to meet the cosmetics 2009 deadline related to acute oral toxicity. Presented at the 15th International Congress on In Vitro Toxicology, Stockholm, Sweden: September 25-28. p. 191.

[10] OECD. 2010. Test Guideline 439: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method. OECD Guideline for the Testing of Chemicals, Section 4. Public web site accessed on August 29, 2012 at http://www.oecd-ilibrary.org/environment/test-no-439-in-vitro-skin-irritation_9789264090958-en;jsessionid=lovzjhjjb3mv.delta.

[11] Aeby P *et al.* 2010. Identifying and characterizing chemical skin sensitizers without animal testing: Colipa's research and method development program. *Toxicol In Vitro.* 24, 1465 – 1473;
Bauch C *et al.* 2011. Intralaboratory validation of four in vitro assays for the prediction of the skin sensitizing potential of chemicals. *Toxicol In Vitro.* 25, 1162–1168;
European Union. 2012. Novel testing strategies for in vitro assessment of allergens, 7th Framework Programme Sens-it-iv. Public web site accessed on August 29, 2012 at http://www.sens-it-iv.eu;
Lambrechts N *et al.* 2010. Assessment of chemical skin sensitizing potency by an in vitro assay based on human dendritic cells. *Tox Sci.* 116(1),122–129;
Kim JM *et al.* 2012. An in vitro method for detecting chemical sensitization using human reconstructed skin models and its applicability to cosmetic, pharmaceutical, and medical device safety testing. *Cutan Ocul Toxicol.*

Overall, we appreciate that CPSC is taking steps to codify a policy related to the use of animal tests and nonanimal alternatives or strategies, and that this Policy includes language to minimize animal testing. However, there are key areas that the CPSC needs to address in order to ensure the greatest possible protections for animals.

We appreciate your consideration of the suggestions in this letter and the Appendices below. Please direct any questions to the undersigned at abirdie@pcrm.org.

Sincerely,

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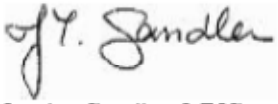

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Appendix A: Specific Text Suggestions – redlined

(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 household products to alert consumers to the potential hazard(s) that the products may present. Among the hazards addressed by the FHSA are acute systemic toxicity, skin and eye corrosivity and irritancy, and dermal sensitization, ~~and irritation~~. 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. Means of characterizing hazards include: prior human experience, literature sources that record the results of prior animal testing or limited human tests, *in silico* and *in vitro* data, weight-of-evidence arguments, and expert opinion.

(2) Neither the FHSA nor the Commission's regulations *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. Historically, animal testing has been used as a proxy for the human reaction, but ~~T~~the Commission ~~also~~ supports animal testing only as a last resort. Therefore, methods of hazard assessment that do not rely on animal testing are preferred, followed by methods that minimize animal use. Finally, if animal testing cannot be avoided, Commission policy advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. Methods that minimize pain and suffering are preferred. 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. ~~These~~ Means of characterizing hazards include: prior human experience, literature sources that record the results of prior animal testing or limited human tests, in silico and *in vitro* data, weight-of-evidence arguments and expert opinion.

~~3) 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) 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. ~~Neither the FHSA nor the Commission's regulations *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to a minimum number of animals, and the policy also advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. 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.~~ In making the appropriate hazard determinations, manufacturers of products subject to the FHSA should use existing alternatives to animal testing, including human data, whenever possible. As in the past, prior human experience shall take precedence over different results from animal data.

~~(4) 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. While animal testing may be necessary in some cases, Commission policy supports limiting such tests to a minimum number of animals, and the policy also advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests.~~

(4) Recommended procedures are summarized in the following statement and can be accessed on the Commission's webpage at: <*web link here*>.

(b) Statement of Policy on Animal Testing

(1) The Commission reviews staff recommendations on alternative test methods developed by the scientific and regulatory communities. Current descriptions of test method recommendations approved by the Commission can be accessed via the Internet at: <*web link here*>. Overall, the Commission prefers test methods that use no animals while maintaining scientific integrity, or, when animal testing is unavoidable minimize the number of animals used and reduce stress and suffering in test animals. ~~and that use none or fewer animals while maintaining scientific integrity. The Commission strongly supports the use of validated alternatives to animal testing.~~ The following parts of this section outline some ~~of these alternatives~~ methods that replace, reduce or refine animal testing. 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 this statement of policy and the regulations under 16 CFR part 1500, should refer to the Commission's animal testing webpage at: <*web link here*>.

(a) Acute toxicity - The ~~traditional~~ historical FHSA animal test for acute toxicity determines the median lethal dose (LD_{50}) or lethal concentration (LC_{50}), the dose or concentration that is expected to kill half the test animals. ~~Procedures for determining the median LD_{50}/LC_{50} are described in section 2(h)(1) of the FHSA and supplemented in §1500.3(c)(1) and (2) and the test method outlined in §1500.40.~~ The traditional LD50 test has proven to be of limited value and is no longer required in pharmaceutical testing. In other regulatory sectors, due to the extreme cruelty of this test, approaches that minimize animal numbers used, or implement a more humane measure of toxicity, have been implemented. The Commission recommends using modifications of the traditional LD_{50}/LC_{50} test during toxicity testing that reduce the number of animals tested, whenever possible. Examples of ~~A~~approved modifications are identified on the web site at: <*web link here*> and include:

(i) *In vitro* and *in vivo* test methods that have been proven 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) An alternate version of the traditional LD50 test that allows for classification of substances based on clear indications of toxicity rather than mortality;

(iv) A sequential version of the traditional LD_{50}/LC_{50} 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;

(~~vi~~v) A limit-dose test, where the LD_{50}/LC_{50} is determined as a point estimate, which can still be used to categorize a hazard, although it gives no information on hazard dose response.

(b) Dermal irritation/corrosivity - A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* dermal irritation testing is considered to determine

appropriate cautionary labeling. This analysis should incorporate any existing data on humans and animals, ~~validated~~ appropriate *in silico* information, *in vitro* test results (~~valid~~ appropriate tests are identified on the Commission's animal testing web site at: <*web link here*>), 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, *in vitro* testing[12] or human patch testing should be considered. If ~~*in vitro* data are unavailable, and~~ human patch testing is not an option, and in rare cases where *in vitro* assessment is not appropriate, a tiered *in vivo* animal test ~~is recommended~~ could be considered. Examples of appropriate approaches are listed on the web site at: <*web link here*>[13].

~~(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 semi-occlusive 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~~ appropriate in silico information, *in vitro* test data (identified on the Commission's animal testing web site at: <*web link here*>), 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 that 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, an ~~Commission-approved~~ *in vitro* assay for ocular irritancy should be run to assess eye irritation potential and determine labeling. ~~Valid~~ Appropriate *in vitro* assays are identified at: <*web link here*>. ~~If~~In rare cases where no ~~a~~ appropriate *in vitro* test exists for the chemical under consideration, an *in vivo* ~~the~~ test strategy for determining dermal corrosion/irritation ~~outlined in section (b)(ii) above~~ can be followed[14]. ~~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~~

[12] OECD Test Guideline 439 In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method.
[13] To facilitate future reductions in animal use, details regarding animal tests should be removed from the policy text and, similar to the alternative approaches, detailed elsewhere (e.g. the web site).
[14] Similar to above, details of animal tests should be given elsewhere.

~~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 considered necessary, 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; (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~~ Examples of specific techniques that have been approved by the Commission in order to minimize both numbers of animals and pain and suffering can be found at: <*web link here*>.

Appendix B: Specific Text Suggestions – clean

(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 household products to alert consumers to the potential hazard(s) that the products may present. Among the hazards addressed by the FHSA are acute systemic toxicity, skin and eye corrosivity and irritancy, and dermal sensitization. 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. Means of characterizing hazards include: prior human experience, literature sources that record the results of prior animal testing or limited human tests, *in silico* and *in vitro* data, weight-of-evidence arguments, and expert opinion.

(2) Neither the FHSA nor the Commission's regulations *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. Historically, animal testing has been used as a proxy for the human reaction, but the Commission supports animal testing only as a last resort. Therefore, methods of hazard assessment that do not rely on animal testing are preferred, followed by methods that minimize animal use. Finally, if animal testing cannot be avoided, Commission policy advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests.

(3) 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. In making the appropriate hazard determinations manufacturers of products subject to the FHSA should use existing alternatives to animal testing, including human data, whenever possible. As in the past, prior human experience shall take precedence over different results from animal data.

(4) Recommended procedures are summarized in the following statement and can be accessed on the Commission's webpage at: <*web link here*>.

(b) Statement of Policy on Animal Testing

(1) The Commission reviews staff recommendations on alternative test methods developed by the scientific and regulatory communities. Current descriptions of test method recommendations approved by the Commission can be accessed via the web site at: <*web link here*>. Overall, the Commission prefers test methods that use no animals while maintaining scientific integrity. When animal testing is unavoidable, the Commission prefers methods that minimize the number of animals used and reduce stress and suffering in test animals. The following parts of this section outline some methods that replace, reduce, or refine animal testing. 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 this statement of policy and the regulations under 16 CFR part 1500, should refer to the Commission's animal testing webpage at: <*web link here*>.

(a) Acute toxicity - The historical FHSA animal test for acute toxicity determines the median lethal dose (LD_{50}) or lethal concentration (LC_{50}), the dose or concentration that is expected to kill half the test animals, section 2(h)(1) of the FHSA and supplemented in §1500.3(c)(1) and (2) and the test method outlined in §1500.40). The traditional LD_{50} test has proven to be of limited value and is no longer required in pharmaceutical testing[14]. In other regulatory sectors, due to the extreme cruelty of this test, approaches that minimize the number of animal used, or implement a more humane measure of toxicity, have been implemented. The Commission recommends using modifications of the traditional LD_{50}/LC_{50} test during toxicity testing that reduce the number of animals tested, whenever possible. Examples of approved modifications are identified on the web site at: <*web link here*> and include:

(i) *In vitro* and *in vivo* test methods that have been proven scientifically appropriate[15];
(ii) Valid *in vitro* methods to estimate a starting dose for an acute *in vivo* test;
(iii) An alternate version of the traditional LD_{50} test that allows for classification of substances based on clear indications of toxicity rather than mortality;
(iv) 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;
(v) 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.

(b) Dermal irritation/corrosivity - A weight-of-evidence analysis is recommended to evaluate existing information before *in vivo* dermal irritation testing is considered to determine appropriate cautionary labeling. This analysis should incorporate any existing data on humans and animals, appropriate *in silico* information, *in vitro* test results (appropriate tests are identified on the Commission's animal testing web site at: <*web link here*>), 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*

[14] ICH. 2009. Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Public web site accessed on August 29, 2012 at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2_Guideline.pdf.

[15] The term "validated" is associated with a complete ICCVAM-like review and can take over a decade to perform and is not appropriate for all testing approaches or regulatory applications. The test or method must be shown to be appropriate for the application and regulatory decision – which may be proven outside of the full ICCVAM validation process (e.g. by independent evaluation, by evaluation by the European Centre for the Validation of Alternative Methods, or by OECD).

vitro, but no data exist regarding its irritation potential, *in vitro* testing[16] or human patch testing should be considered. If human patch testing is not an option, and in rare cases where *in vitro* assessment is not appropriate, a tiered *in vivo* animal test could be considered. Examples of appropriate approaches are listed on the web site at: <*web link here*>.

(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, appropriate *in silico* information, *in vitro* test data (identified on the Commission's animal testing web site at: <*web link here*>), 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 that the substance might be a dermal corrosive or irritant or ocular irritant. When the weight-of-evidence is insufficient to determine a substance's ocular irritation, an *in vitro* assay for ocular irritancy should be run to assess eye irritation potential and determine labeling. Appropriate *in vitro* assays are identified at: <*web link here*>. In rare cases where no appropriate *in vitro* test exists for the chemical under consideration, an *in vivo* test strategy for determining dermal corrosion/irritation can be followed. Examples of specific techniques that have been approved by the Commission in order to minimize both numbers of animals and pain and suffering can be found at: <*web link here*>.

PUBLIC SUBMISSION

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Codification of Animal Testing Policy
Comment On: CPSC-2012-0037-0001
Codification of Animal Testing Policy
Document: CPSC-2012-0037-0002
Comment from Jean Public

Submitter Information
Name: Jean Public
Submitter's Representative: NONE
Organization: NONE

General Comment
NO RABBITS SHOULD EVER BE USED. THIS CODIFICATION SHOULD TAKE RABBITS OUT AND SPECIFICALLY STATE RABBITS SHOULD NEVER BE USED IN ANY OF THIS TESTING. THIS CODIFICATION SHOULD STATE THAT TESTING ON PEOPLE OR HUMAN CELLS IS THE PREFERRED METHODS. RABBITS SHOUDL BE TAKEN FROM THE LIST OF ANIMALS THAT ARE USED FOR ANY TESTING. NO MORE RABBITS SHOULD BE USED AT ANY TIME. ALSO THI SCHANGE SHOULD REFLECT THAT THIS AGENCY PREFERS OTHER TEST METHODS THATN ABUSIVE TESTS ON ANIMALS. TESTS ON HUMAN CELLS OR ONPEOPLE ARE PREFERRED. IT IS ALSO CLEAR THAT TESTS TESTS ON ANIMALS ARE DECEPTIVE AND NOT REALLY RELEVANT OR MEANINGFUL IN APPLICATION TO WHAT THE PRODUCT WILL DO TO A PERSON. AGAIN, GET THE RABBITS ENTIRE OUT OF THIS TESTING CYCLE. THIS TEST METHOD STARTED IN MIDIEVEL TIMES 1500 AD. WE HAVE MUCH MORE RELIABLE METHODS OF TESTING TODAY THAN ABUSING AND PAINFULLY INJURING AND KILLING RABBITS. More rabbits are used for research in the U.S. than any other covered species. In 1987, an all-time high of 554,385 rabbits were exploited for research and testing.
Rabbits are widely used for experimentation and testing mainly due to practical rather than scientific considerations. They are small and usually docile, easily restrained, and breed prodigiously. s. The tests KNOWN AS the Draize eye and skin irritancy tests, are extremely painful and cruel. While being experimented upon, rabbits are also often locked into full-body restraints to prevent them from touching eye or skin sores. These tests are not very reliable, and increasing attention is being paid to the development of alternatives to replace the use of rabbits for these categories of toxicity testing.

TAB C: CHANGES MADE TO THE NPR AND STATEMENT OF POLICY BASED ON PUBLIC COMMENTS ON FR VOL. 77, NUM. 126

NPR Revisions

1) **Amend § 1500.3(c)(1)**

Section 1500.3(c)(1) of 16 CFR supplements the statutory definition of the *highly toxic* category presented in the FHSA and §1500.3(b). The FHSA requires specific labeling for *highly toxic* substances or mixtures of substances and different labeling for *toxic* substances. For an orally toxic substance, for example, the term *highly toxic* is defined in 16 CFR § 1500.3(b) as "*any substance which falls within any of the following categories: (a) Produces death within fourteen days in half or more than half of a group of ten or more laboratory white rats each weighing between two hundred and three hundred grams, at a single dose of fifty milligrams or less per kilogram of body weight, when orally administered ....*" The subsequent definitions for "inhaled and dermally toxic substances" are similar. In 16 CFR §1500.3(c)(1), the definition is supplemented to give alternatives to the number of animals tested. It states: "*The number of animals tested shall be sufficient to give a statistically significant result and shall be in conformity with good pharmacological practices.*" Both the Act at 2(h)(2) and the supplemental definition state that available data on human experience that indicate results different from those obtained in animals in the defined dosages or concentrations will always take precedence.

Acute toxicity testing in animals is typically the initial step in evaluating the health effects of a substance and is generally defined as adverse health effects occurring within a short time (up to ~14 days) of administration of a single dose of a substance or multiple doses given within 24 hours. Animals can be exposed to substances orally, by inhalation, or dermally. Conventional tests for acute oral toxicity focus on determining the median lethal dose (LD_{50}), the dose that is expected to kill half the tested animals. The median lethal dose is a statistically derived value, and in the past, tests might have used as many as 100 animals. As discussed previously, however, more recently developed methods use fewer animals, no animals at all, and/or have been broadened to include endpoints other than lethality.

Staff agrees that the methods in §1500.3(c)(1)(ii) A–C, used in the definitions of "oral," "inhalation," and "dermal" toxicity, respectively, each describe one way of testing; and hence, define a substance as *highly toxic.* However, staff does not believe that a single method of testing should be presented as a definition because it could imply that the described method is the only means of testing and defining a product's toxicity under the FHSA or that this may be the only method the CPSC uses to make assessments of product toxicity. Based on the supplementary definition of *highly toxic,* as long as a scientifically valid method is used to determine the LD_{50}, the number of animals and the method itself is not predetermined.

Therefore, staff recommends changing §1500.3(c)(1) by appending part (iii) (underlined parts are new text):

> (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:

(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 shall be sufficient to give a statistically significant result and shall be in conformity with good pharmacological practices.

(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) Amend § 1500.3(c)(2)

16 CFR §1500.3(c)(2) supplements the statutory definition of the *toxic* category presented in the FHSA and §1500.3(b). As with *highly toxic*, the label *toxic* is defined supplementarily as a specific outcome of the LD_{50} test described in §1500.3(c)(2)(i)(A-C). Staff recommends adding prior human experience to the first part of the definition of toxic, consistent with the previous section. Staff further recommends appending a sentence at the end of §1500.3(c)(2)(i) to indicate that there are other methods for toxicity testing and defining a substance *toxic* that may be acceptable to the Commission, and that guidance for these can be found in the CPSC's animal testing policy. Hence, the amended §1500.3(c)(2) will read as follows (underlined parts to be added to existing text):

(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) Acute toxicity. Toxic means 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 from 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.

~~(iii)~~ *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.

~~(~~ii) Chronic toxicity. A substance is toxic because it presents a chronic hazard if…

3) Amend § 1500.3(c)(3)

16 CFR §1500.3(c)(3) supplements the FHSA definition of *corrosive.* The supplemental definition references human experience, as well as animal testing and reads: "*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 technique described in §1500.41is a test for acute dermal toxicity. Staff would change this definition

so that §1500.41 is not the only nonhuman testing method mentioned because this implies it is the only method used or accepted by the CPSC, or at least the preferred method.

Staff recommends amending §1500.3(c)(3) in this way (underlined parts to be added to existing text):

> (3) The definition of corrosive in section 2(i) of the act (restated in paragraph (b)(7) of this section) is interpreted to also mean the following: 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 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) Amend § 1500.3(c)(4)

This section supplements the FHSA definitions of *irritant*, *primary irritant*, and *eye irritant* using references to §1500.41 and §1500.42, which each describe a specific animal test method and outcome. Staff does not believe these terms should be defined *only* on the basis of these specific animal tests because there are other scientifically valid ways of testing for irritancy that may be used by the CPSC or the public, including methods that do not use animals.

Therefore, staff recommends amending § 1500.3(c)(4), as follows (underlined parts to be added to existing text):

> (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 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 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) Amend § 1500.40: Method of Testing Toxic Substances

This section comprises a detailed description of an acute dermal toxicity assay using rabbits. The method is referenced in § 1500.3(c)(1)(ii)(C) and 2(iii). Staff agrees that the method described in §1500.40 is one way of assessing a substance's acute dermal toxicity. However, staff does not wish to imply that this is the only or preferred method for evaluating dermal toxicity; nor does it wish to convey that animal testing is mandatory.

Therefore, staff recommends changing the beginning of this section, as follows (underlined parts to be added to existing text):

> Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy. 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~~ If *in vivo* testing is ~~necessary~~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 . . .

6) Amend § 1500.41: Method of Testing Primary Irritant Substances

Section 1500.41 of 16 CFR comprises a detailed description of a primary irritation assay that uses rabbits. The method is referenced in definition §§1500.3(c)(3) and 1500.3(c)(4). Staff agrees that the method described in §1500.41 is one way of assessing a substance's dermal irritation/corrosivity. However, staff does not wish to imply that this is the only or preferred method for such an evaluation; nor does staff wish to imply that animal testing is mandatory.

Therefore, staff recommends changing the beginning of this part, as follows (underlined parts to be added to existing text):

> 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. ~~When~~ If *in vivo* testing is ~~necessary~~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) Amend § 1500.42: Test for Eye Irritants

Section 1500.42 of 16 CFR is a detailed animal test for eye irritation. The method is referenced in §1500.3(c)(4), which defines *irritation*. Staff agrees that the method described in §1500.42 is one way of assessing a substance's properties of ocular irritation.

Because staff does not think this is the only or the preferred method for such an evaluation, staff recommends changing the part immediately after the heading titled, "Test for eye irritants" as follows (underlined parts to be added to existing text):

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. ~~When~~ If *in vivo* testing is ~~necessary~~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) Amend § 1500.42(c): Nonsubstantive Change

Staff recommends replacing the reference in §1500.42(c) to the "Illustrated Guide for Grading Eye Irritation by Hazardous Substances," with a reference to the CPSC's proposed new animal testing policy Web page. The referenced guide is out of print, and photocopies are rare. To assist testing laboratories and others interested in interpreting ocular irritation test results, the proposed rule amends §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 will contain the scoring

system defined in the U.S. EPA's Test Guideline, OPPTS 870.2400: Acute Eye Irritation[2] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[3]

[2] 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)

[3] 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)

Revisions to Staff's Proposed Statement of Policy on Animal Testing, 2012

(a) Summary

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.

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.

However, neither the FHSA, nor the Commission's regulations *require* animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. ~~While~~ If animal testing ~~may be~~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.

Therefore, 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). 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, 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 *require* animal testing. Reliable human experience always takes precedence over results from animal data. In the cases where animal

tests are ~~necessary~~ 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 ~~validated~~ 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 (LD_{50}) or lethal concentration (LC_{50}), the dose or concentration that is expected to kill half the test animals. Procedures for determining the median LD_{50} /LC_{50} 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* LD_{50}/LC_{50} tests, or using modifications of the traditional LD_{50}/LC_{50} test during toxicity testing that reduce the number of animals tested whenever possible. ~~Approved~~ 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 LD_{50} /LC_{50} 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 LD_{50}/LC_{50} 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 LD_{50} 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 animal tested from the 80 to 100 animals involved in a full LD_{50} test to, typically, 10 to 20 rats per product. This reduction in the number of animals tested is justified because an exact LD_{50} 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 ~~considered necessary~~ 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.

TAB D: REGULATORY IMPACT ANALYSIS

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

Memorandum

Date: October 10, 2012

TO : Leslie E. Patton, Ph.D., Toxicologist, Directorate for Health Sciences

THROUGH : Gregory B. Rodgers, Ph.D., Associate Executive Director, Directorate for Economic Analysis
Deborah V. Aiken, Ph.D., Senior Staff Coordinator, Directorate for Economic Analysis

FROM : Charles L. Smith, Directorate for Economic Analysis

SUBJECT: Final Regulatory Analysis: Amendments to *Hazardous Substances and Articles; Administration and Enforcement Regulations*, 16 CFR Part 1500

In the June 29, 2012 *Federal Register*, the U.S. Consumer Product Safety Commission (CPSC, Commission) published proposed amendments to *Hazardous Substances and Articles; Administration and Enforcement Regulations* under the Federal Hazardous Substances Act (FHSA). The amendments are proposed in conjunction with the animal testing policy for determining hazardous substances defined under the FHSA. An update is needed to amend sections of the Code of Federal Regulations (CFR) that contain outdated or incomplete information on animal testing. The CPSC's animal testing policy has not been formally updated since 1984. Recent innovations in hazard testing focus on the reduction or replacement of animals in testing, and the refinement of techniques that alleviate or minimize pain, distress, and/or suffering to animals, while maintaining scientific quality and protecting public health.

This memorandum presents the final regulatory analysis for the amendments to the FHSA regulations that update the Commission's regulations related to animal testing. In summary, the findings of the September 19, 2011 preliminary regulatory analysis for the rule remain unchanged.

Amendments to *Hazardous Substances and Articles; Administration and Enforcement Regulations*

The substantive changes, and staff's rationale for each change, are summarized below:

1) Amend § 1500.3(c)(1–4): Definitions
Staff recommends that CPSC's proposed new animal testing policy be referenced in the statutory definitions of "highly toxic," in §1500.3(c)(1); "toxic," in §1500.3(c)(2); "corrosive," in §1500.3(c)(3); "irritant, primary irritant, and eye irritant," in §1500.3(c)(4).

2) Amend §1500.40: Method of Testing Toxic Substances

This section provides a detailed description of an acute dermal toxicity assay using rabbits. The method is referenced in § 1500.3(c)(1)(ii)(C) and 2(iii). Staff agrees that the method described in §1500.40 is one way of assessing a substance's acute dermal toxicity, when animal testing has been deemed necessary. However, staff does not wish to imply that this is the only or preferred method for evaluating dermal toxicity; nor does it wish to convey that animal testing is mandatory.

Therefore, staff recommends changing the beginning of this section as follows (underlined parts to be added to existing text):

> 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 . . .

3) Amend § 1500.41: Method of Testing Primary Irritant Substances

Section 1500.41 of 16 CFR provides a detailed description of a primary irritation assay that uses rabbits. Staff agrees that the method described in §1500.41 is one way of assessing a substance's dermal irritation/corrosivity. However, staff does not wish to imply that this is the only or preferred method for such an evaluation.

Therefore, staff recommends changing the beginning of this part as follows (underlined parts to be added to existing text):

> 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. ...

4) Amend §1500.42: Test for Eye Irritants

Section 1500.42 of 16 CFR is a detailed animal test for eye irritation. Staff agrees that the method described in §1500.42 is one way of assessing a substance's properties of ocular

irritation. Staff does not think this is the only or the preferred method for such an evaluation and it recommends changing the beginning of this section as follows (underlined parts to be added to existing text):

> 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 chemicals 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 are 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 . . ..

5) Amend §1500.42(c): Nonsubstantive Change:
Staff recommends replacing the reference in §1500.42(c) to the "Illustrated Guide for Grading Eye Irritation by Hazardous Substances" with a reference to the CPSC's proposed new animal testing policy Web page. The referenced guide is out of print, and photocopies are rare. To assist testing laboratories and others interested in interpreting ocular irritation test results, the proposed rule amends §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 will contain the scoring system defined in the U.S. EPA's Test Guideline, OPPTS 870.2400: Acute Eye Irritation[4] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[5]

Requirements that Must Be Met Under the FHSA and Other Governing Laws

Under the Regulatory Flexibility Act of 1980 (RFA), the Commission is required to address the potential economic effects of a proposed rule on small businesses and other small

[4] 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)

[5] 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)

entities. Also, under the National Environmental Policy Act (NEPA), the Commission is required to consider the potential environmental effects of the proposed rule.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) requires that the Commission consider whether a rule would have a significant economic effect on a substantial number of small entities, including small businesses and small government entities. There should be little or no effect on small businesses because the amendments will not result in product modifications in order to comply and will not result in additional testing or recordkeeping burdens. If anything, the clarifications resulting from the amendments will likely result in cost savings to small businesses because the rule changes more clearly define circumstances where testing on animals can be omitted. Therefore, the Commission could conclude that the amendments to the *Hazardous Substances and Articles; Administration and Enforcement Regulations* (16 CFR part 1500) are not expected to have a significant economic effect on a substantial number of small entities.

National Environmental Policy Act (NEPA)

Under NEPA, the Commission is required to consider the potential environmental impacts that would result from a rule. The amendments should not have an impact on the production processes used by manufacturers. There is also no expected impact on the amounts of materials used in manufacture, packaging, or labeling. It would not render existing finished goods inventories, or works in progress, unsellable, nor require destruction of these products. Therefore, the rule should not have adverse environmental consequences.