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

This document has been electronically approved and signed.

**BALLOT VOTE SHEET**

Date: June 13, 2012

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Cheryl A. Falvey, General Counsel
Kenneth R. Hinson, Executive Director

FROM : Hyun S. Kim, Acting Assistant General Counsel

SUBJECT : Notice of Proposed Rule – Revisions to Animal Testing Regulations and Proposed Codification of Animal Testing Policy

**BALLOT VOTE Due:** June 19, 2012

Attached are the following draft *Federal Register* notices for Commission consideration: (A) notice of proposed rulemaking to amend 16 CFR part 1500, to reflect changes to the CPSC's animal testing regulations; and (B) proposed codification of the CPSC's animal testing policy.

A. Please indicate your vote on the following options on the notice of proposed rulemaking:

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.)

_____

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_____

_____ _____
(Signature) (Date)



THIS DOCUMENT HAS NOT BEEN REVIEWED OR ACCEPTED BY THE COMMISSION.

CLEARED FOR PUBLIC RELEASE UNDER CPSA 6(b)(1)

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

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

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_____ _____
(Signature) (Date)

B. Please indicate your vote on the following options on the proposed 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.)

_____

_____

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_____ _____
(Signature) (Date)



THIS DOCUMENT HAS NOT BEEN REVIEWED
OR ACCEPTED BY THE COMMISSION.

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UNDER CPSA 6(b)(1)

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

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

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_____ _____
(Signature) (Date)

Attachments: Draft *Federal Register* notices: (1) Notice of Proposed Rulemaking-Revisions to Animal Testing Regulations; (2) Codification of Animal Testing Policy

CPSC staff memorandum on Revision of Animal Testing Sections of 16 CFR Part 1500



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**[Billing Code 6355-01-P]**

**CONSUMER PRODUCT SAFETY COMMISSION**

**[CPSC Docket No. CPSC-2012- ]**

**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 16 CFR part 1500 to update regulations on the CPSC's animal testing methods under the Federal Hazardous Substances Act (FHSA).

**DATES:** Written comments must be received by **[insert date that is 75 days after publication in the Federal Register**].

**ADDRESSES:** You may submit comments identified by [Docket No. CPSC-2012----], 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 (e-mail) except through www.regulations.gov.

Written Submissions

Submit written submissions in the following way:

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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 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) 504-7848; 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

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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 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 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 (Public Law 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

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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 website 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'statement of policy on animal testing published elsewhere in this *Federal Register*, the proposed rule adds language under new section1500.3(c)(1)(iii) as follows : <u>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</u>.

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 : <u>*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.</u>

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.

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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 <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>

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.

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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)(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; <u>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.</u> *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; <u>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.</u>

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":

> <u>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.</u>

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":

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> 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 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]

**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

[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 )



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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.

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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

2. Amend section1500.3 by adding a 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

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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, physicochemical 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. Before the first sentence in section 1500.41, add the following:

**§ 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,

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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. * * *

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 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 will contain the scoring

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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

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[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- ]**

**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* on May 30, 1984 (49 FR 22522). 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 [**insert date that is 75 days after publication in the Federal Register**].

**ADDRESSES:** You may submit comments, identified by Docket No. [CPSC-2012- ], 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 (e-mail) except through www.regulations.gov.

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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 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) 504-7848; 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

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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 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 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

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since the National Institutes of Health Revitalization Act was passed in 1993 (Public Law 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

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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 website 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]**

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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 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

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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 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 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

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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 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 website at: <*web link here*> 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;

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(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 website 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, 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.

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(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 website 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, 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: <*web link here*>. If no valid *in vitro* test exists, the test strategy for determining dermal corrosion/irritation

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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: <*web link here*>.

Dated: _____

_____
Todd A. Stevenson, Secretary
Consumer Product Safety Commission

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

This document has been electronically approved and signed.

**Memorandum**

June 13, 2012

TO: The Commission
Todd A. Stevenson, Secretary

THROUGH: Cheryl A. Falvey, 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 Proposed Codification of Animal Testing Policy

## I. INTRODUCTION

This memorandum presents U.S. Consumer Product Safety Commission (CPSC) staff's recommendation to publish a notice of proposed rulemaking (NPR) to amend the CPSC's animal testing policy that is used in determining cautionary labeling for hazardous substances under the Federal Hazardous Substances Act (FHSA). 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.

In addition to updating sections of 16 CFR part 1500 that contain outdated or incomplete information on animal testing, staff recommends that the Commission codify an updated policy on animal testing that provides for the use of new technologies and advances, as well as existing methods. The CPSC's animal testing policy has not been formally updated since 1984. 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. Although not a new area for the CPSC, alternatives to the use of animals in toxicity testing currently is an important domestic and international topic that deserves the attention of the regulatory community in the United States, and it is particularly important for the CPSC in its role of enforcing the FHSA. CPSC staff believes that updating and codifying this policy is important because many people outside the agency, including other federal and international regulatory bodies, are unaware of, or misunderstand, the CPSC's policy on the use of animals in toxicity testing, particularly holding the erroneous notion that the FHSA *requires* animals in toxicity testing. Therefore, CPSC staff would like to update this policy to serve as a clear explanation of the agency's animal testing policy. Additionally, CPSC staff recommends that the Commission establish a public Web page that will maintain a transparent, current description of the CPSC's animal testing policy, including Commission approvals of relevant



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recommendations. Finally, this effort is being carried out as part of the CPSC's ongoing commitment to retrospective rule review, in which we seek to change or remove aspects of our rules that are, among other things, outdated or inefficient, while maintain high standards for consumer safety.

## II. BACKGROUND

Precautionary labeling of hazardous household substances is mandated by the Federal Hazardous Substances Act (FHSA), 15 U.S.C. §1261–1278. Under the FHSA, to be a hazardous substance, a product must present one or more of the hazards enumerated in the statute, and it must have the potential to cause substantial personal injury or substantial illness during, or as a result of, any customary or reasonably foreseeable handling or use, including ingestion by children. Hazards such as eye and skin irritancy, tissue corrosivity, and toxicity are based on biological response of living tissue and organs. Under the FHSA, animal testing is not mandatory, but rather, an option to use in determining the biological response and the appropriate cautionary labeling for a consumer product. Brief descriptions of animal test methods used to aid in the classification of substances as hazardous, based on toxicity, corrosivity, and irritation, are provided in the FHSA and in 16 CFR part 1500. For example, the test method for assessing acute dermal toxicity in rabbits is detailed in § 1500.40. Sections 1500.41 and 1500.42 describe animal test methods for primary skin and eye irritants, respectively. Sections 1500.3(c)(1) and (2) define *severely toxic* and *toxic*, nearly exclusively with respect to the outcomes of the acute animal toxicity tests that are described in those sections. Sections 1500.3(c)(3), (4), and (5), respectively, define *corrosive, irritant,* and *strong sensitizer* with some specific reference to animal testing. Similarly, the chronic hazard guidelines,[1] published in a *Federal Register* notice dated October 9, 1992, and summarized in 16 CFR §§ 1500.3(c)(2)(ii) and 1500.135, include a general reference to animal testing.

In 1984, the Commission adopted, but did not codify, a policy for animal testing that minimized the number of test animals required for toxicity testing and clarified when animal testing might be needed (49 FR 22522; see Tab A of this memorandum). These guidelines advise product manufacturers to use alternatives to animal testing whenever possible, specifically suggesting the use of: (1) prior human experience, (2) existing animal or human test results, and (3) expert opinion. For example, the policy states that a product known to be a primary skin irritant does not have to be tested for eye irritation because these properties are usually correlated. The Commission currently recommends animal testing only when information and data sources have been exhausted; the FHSA states that human experience takes precedence over animal data. The 1984 policy recommends using laboratory animals in a tiered- and sequential-testing approach, which can effectively reduce the number of animals used. In a tiered-testing

[1] The chronic hazard guidelines established methods by which CPSC staff assesses chronic hazards associated with chemicals in consumer products under the FHSA. CPSC staff uses the chronic hazard guidelines when evaluating chemicals for chronic hazards, including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, and risk. These guidelines provide default assumptions that can be made in the course of evaluating chronic hazards when actual data are not available.



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strategy, the substance is tested *in vivo,*[2] if the appropriate hazard determination cannot be made from a weight-of-evidence analysis of existing data and other information. The policy describes the procedures staff had in place in 1984, when animal testing was needed. The procedures reduced the number of test animals in traditional acute toxicity tests and eye irritation assays; and additional animals are only tested based on the results of the first test. The CPSC's 1984 policy also emphasizes taking measures to lower the pain and suffering associated with testing. For example, the policy gives guidance on using two applications of tetracaine (an ophthalmic analgesic) in the eyes of rabbits prior to ocular irritation testing and allows the animals to move about freely. This eliminated the use of a device that immobilized animals during testing.

## III. DISCUSSION

### A. Recent Developments in Animal Testing Alternatives - ICCVAM

When new methods are accepted by the scientific community as replacements or adjuncts to animal tests for predictions of toxicity and irritancy, the CPSC's 1984 animal testing policy states that "Health Sciences will incorporate the techniques into the Commission's compliance program . . . 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." Such developments in testing have been produced in recent years, particularly since the National Institutes of Health Revitalization Act was passed in 1993, 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 (Public Law No. 103-43, Section 1301).

To accomplish these goals, NIEHS created an *ad hoc* 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. The Committee comprises 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. Stakeholders from government, industry, or academia carry out research, development, and validation of alternative acute or chronic toxicity studies and submit these to ICCVAM for evaluation. ICCVAM develops its own recommendations on the scientific validity of the test methods, and then it submits recommendations to federal agencies for acceptance. 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 under the mandate of the ICCVAM Authorization Act of 2000. Federal agencies have 180 days from the time of ICCVAM's submission to identify any relevant test methods for which the

[2] In the living organism.



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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 voted on seven recommendations (see Table 1 below) made by ICCVAM to reduce and refine animal testing. After receiving recommendations from ICCVAM, CPSC staff considers the strengths and weaknesses of each recommendation and the relevance of each to the FHSA. As such, test method recommendations may be accepted in their entirety as submitted, but if only limited applications of the test method exist that are relevant to the FHSA, CPSC staff will modify their recommendation accordingly. For example, in accepting the ICCVAM recommendation on the reduced Local Lymph Node Assay test method for dermal sensitizers (March 2010), CPSC staff noted that this method would fit into a weight-of-evidence evaluation under the FHSA but was relevant only for use in cases where dose-response information is not needed. Similarly, in the 2010 ocular testing recommendation package (see 3/2/11 in Table 1 below) received from ICCVAM, [3] CPSC staff considered only three of the four recommendations included in that package because one (the current validation status of a proposed *in vitro* testing strategy for the U.S. Environmental Protection Agency ocular hazard classification and labeling of antimicrobial cleaning products) was deemed irrelevant to the CPSC's mission because it dealt with products not under the jurisdiction of the FHSA.

The ICCVAM documents referred to in Table 1 currently are available through the CPSC's website only, by searching in the CPSC's online FOIA library by title for "ICCVAM" or by topic for "animal alternatives" (see http://www.cpsc.gov/library/foia/foialook.html).

Additional recommendations from ICCVAM are anticipated on an ongoing basis.

[3] Birnbaum, L.S. 2010. Transmittal letter on behalf of ICCVAM to CPSC Chairman Inez Tenenbaum, requesting agency response to test method recommendations from ICCVAM. September 2, 2010. Available: http://iccvam.niehs.nih.gov/methods/ocutox/transmit2010/Tenenbaum.pdf



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| Table 1: List of Commission Votes Pertinent to Animal Testing Policy | | |
|---|---|---|
| **Date** | **Vote Item** | **Vote Outcome** |
| 8/29/03 | Recommended response to ICCVAM on acute toxicity testing: (1) the revised Up-and-Down Procedure (UDP) for determining acute oral toxicity for the purpose of classification and labeling, and (2) *in vitro* methods for determining the starting dose for acute systemic toxicity testing. | Accepted |
| 1/29/08 | Staff recommendation on response to ICCVAM on four *in vitro* ocular toxicity test methods: (1) the isolated rabbit eye (IRE) test; (2) the isolated chicken eye (ICE) test; (3) the bovine corneal opacity and permeability (BCOP) test; and (4) the hen's egg test - chorioallantoic (HET-CAM). | Accepted |
| 8/28/08 | Staff recommendation on response to ICCVAM on the use of *in vitro* basal cytotoxicity test methods for estimating starting doses for acute oral systemic toxicity testing | Accepted |
| 1/5/09 | Staff response to ICCVAM recommendations for five *in vitro* methods for assessing pyrogenicity of pharmaceuticals and other products. | Determined irrelevant to consumer products/CPSC mission |
| 3/9/10 | Staff recommendation on response to ICCVAM revisions to the murine local lymph node assay: (1) updates to the test method protocol; (2) establishment of performance standards; and (3) a modified form of the assay, the reduced Local Lymph Node Assay (rLLNA). | Accepted |
| 1/26/11 | Staff response to ICCVAM recommendations on revisions to the murine local lymph node assay: (1) the Bromodeoxyuridine Enzyme-linked Immunosorbent Assay (BrdU-ELISA); (2) the Daicel Chemical Industries version (LLNA:DA); and (3) an update on the LLNA's applicability domain, particularly its effectiveness in testing pesticide formulations, metals, and substances in aqueous solutions | Accepted |
| 3/2/11 | Staff response to ICCVAM recommendations on four test method evaluation reports regarding ocular toxicity testing: (1) the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing; (2) the current validation status of five *in vitro* test methods proposed for identifying eye injury hazard potential of chemicals and products; (3) the discontinuation of the use of the low volume eye test for ocular safety testing; and (4) the current validation status of a proposed *in vitro* testing strategy for the U.S. Environmental Protection Agency ocular hazard classification and labeling of antimicrobial cleaning products. | 3 of 4 Accepted; one not considered because determined irrelevant to CPSC mission |

### B. Recent Development in Animal Testing Alternatives – OECD

Like ICCVAM, the international scientific community is regularly developing guidelines for alternative tests. The Organization for Economic Cooperation and Development (OECD) reviews and validates test method guidelines for chemicals, including those for irritation, corrosivity, and acute toxicity. The OECD Test Guidelines Program formally established an interagency group in 2002, dedicated to the validation and acceptance of internationally harmonized non-animal test methods. Validation of a proposed test method under the OECD's



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program contributes to its international acceptance and supports the policy of Mutual Acceptance of Data (MAD). [4] OECD member countries, like the United States, can accept data that comply with OECD Test Guidelines and Principles of Good Laboratory Practice. For example, the CPSC can consider such data in making a hazard determination; however, the CPSC's acceptance of data from harmonized methods is not automatic and may be contingent on the need for a more detailed review by the Commission or staff.

Despite these new scientific developments and policy focus on alternative testing methods, the CPSC has never amended sections of 16 CFR part 1500 that describe and recommend toxicity tests, nor has it codified any animal testing policy since the inception of the FHSA.

## IV. STAFF CONCLUSIONS

On March 2, 2011, the Commission directed staff to update the CPSC's animal testing policy for hazardous substances regulated under the FHSA. [5] The CPSC's animal testing policy has not been formally updated since 1984, at which time an uncodified policy urged staff to review and incorporate new testing methods into existing policy. Staff proposes amendments to the CPSC's animal testing policy for hazardous substances regulated under the FHSA. Staff concludes that 16 CFR part 1500 should be amended by revising outdated sections pertaining to animal testing.

Staff further proposes to codify a statement of CPSC's policy on animal testing that will serve to clarify these regulations. Staff believes that codification of this policy will allow better public access to the guidance in connection with the applicable regulations in the CFR. The proposed statement of policy, provided in Tab C of this memorandum, is a set of guidelines comprising methodological changes that potentially will reduce the number of test animals, lower pain and suffering associated with testing, and it reiterates that human experience, existing animal or human test results, and expert opinion are preferred alternatives to animal testing. When valid alternatives to animal testing have been exhausted, guidelines recommend tiered- and sequential-animal testing strategies that potentially will reduce the number of test animals required to classify substances as hazardous, based on toxicity, corrosivity, and irritation.

In order to provide the public with access to any developments related to animal testing, CPSC staff believes that the CPSC's animal testing policy should be publically available on a

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[4] The MAD policy was adopted by OECD member countries, including the United States, in a 1981 OECD Council Act. The policy states: "data generated in a Member country in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) shall be accepted in other Member countries for assessment purposes and other uses relating to the protection of human health and the environment" (OECD website: http://www.oecd.org/document/41/0,3343,en_2649_201185_1890473_1_1_1_1,00.html).

[5] *Record of Commission Action on the Staff Response to the ICCVAM Recommendations on Four Test Method Evaluation Reports Regarding Ocular Toxicity Testing.* Commission ballot vote, March 2, 2011. Available: http://www.cpsc.gov/library/foia/ballot/ballot11/oculartoxRCA.pdf



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new CPSC animal testing policy Web page dedicated to the subject. Development of a public Web page will maintain a transparent, current description of the CPSC's animal testing policy, including the outcome of Commission votes on alternative test methods, such as those shown in Table 1, as well as direct Web links to ICCVAM recommendations and the Commission's responses.

## V. STAFF RECOMMENDATIONS TO REVISE 16 CFR PART 1500

CPSC staff recommends that the Commission revise 16 CFR part 1500, *Hazardous Substances and Articles; Administration and Enforcement Regulations,* as follows:

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 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



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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 to be added to existing text):

> (1) To provide flexibility as to the number of animals tested, 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.
> <u>(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.</u>

**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) and begins: "*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 ....*" It also states: "*The number of animals tested shall be sufficient to give a statistically significant result and shall be in conformity with good pharmacological practices." Toxic* also applies to any substance that is *toxic* (but not *highly toxic)* on the basis of human experience. Also, §1500.3(c)(2) states 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.

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). Staff recommends appending a sentence at the end



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of this section to indicate that there may be other Commission-approved methods that may be used by CPSC staff or the public for toxicity testing and defining a substance *toxic,* and that guidance for these can be found in the CPSC's animal testing policy.

Therefore, staff recommends amending §1500.3(c)(2) by appending part (iii) (underlined parts to be added to existing text):

> (iii) <u>*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.</u>
>
> .

**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):

> 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 <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>
>
> .



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**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):

> 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; <u>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.</u> 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; <u>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.</u>

**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):

> <u>Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy</u>. <u>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</u>



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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 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) 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 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



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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[6] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[7]

[6] 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 )

[7] 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 )



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## VI. ECONOMIC AND ENVIRONMENTAL IMPACT (TAB B)

**1) Economic Impact**

The Regulatory Flexibility Act (RFA) requires that the Commission consider whether a proposed rule would have a significant economic effect on a substantial number of small entities. Based on available information, CPSC staff believes that there would be little or no effect on small businesses and other entities because CPSC staff's suggested amendments will not result in product modifications in order to comply, and they will not result in additional testing or recordkeeping burdens (TAB B). Therefore, the Commission could conclude 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 have a significant economic effect on a substantial number of small entities.

**2) Environmental Impact**

Under the National Environmental Policy Act (NEPA), the Commission is required to consider the potential environmental impacts that would result from a proposed rule. CPSC staff does not believe that the proposed rule will have adverse environmental consequences (TAB B). Therefore, the Commission could conclude that the amendments to the *Hazardous Substances and Articles; Administration and Enforcement Regulations* (16 CFR part 1500) recommended by CPSC staff should not have adverse environmental consequences.

## VII. STAFF RECOMMENDATIONS TO CODIFY POLICY FOR ANIMAL TESTING

CPSC staff recommends that the Commission approve codification in the CFR of the proposed updated policy for animal testing.

CPSC staff recommends that the Commission approve the development of a new CPSC animal testing policy Web page that provides the public with the CPSC's updated, codified animal testing policy and new developments and the Commission's approvals of alternative test methods, such as those recommended by ICCVAM.



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# TAB A. 49 FR22522: 1984 CPSC ANIMAL TESTING POLICY



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The following text is the CPSC animal testing policy that was published in the *Federal Register* volume 49, no. 105 (pp. 22522–22523), on Wednesday, May 30, 1984.

**CONSUMER PRODUCT SAFETY COMMISSION**

**Animal Testing Policy**
**Agency:** Consumer Product Safety Commission
**Action**: Notice.

**Summary**: The Commission publishes a statement of its policy concerning animal testing in order to inform interested persons and to encourage manufacturers of products subject to the Federal Hazardous Substances Act to adopt a similar policy, which is intended to reduce the number of animals tested to determine hazards associated with household products and to reduce any pain that might be associated with such testing.

**SUPPLEMENTARY INFORMATION**: As explained in more detail in the statement set forth below, animal testing is sometimes performed by the Commission or by manufacturers of products subject to the Federal Hazardous Substances Act (FHSA), 15 U.S.C. 1261-1275, to determine hazards associated with such products. The Commission has adopted policies intended to minimize the number of animals tested and to reduce the pain associated with such tests. This notice is published in order to inform interested members of the public of the Commission's policy and to correct possible misinterpretations of the requirements of the FHSA, and the Commission's regulations under that act, that concern animal testing.

**CPSC Policy on Animal Testing**

The Federal Hazardous Substances Act (FHSA) 15 U.S.C. 1261-1275, is one of the laws administered by the Consumer Product Safety Commission (Commission). One of the primary functions of this law is to require appropriate cautionary labeling on certain hazardous household products to alert consumers to the potential hazards the products may present. Among the hazards addressed by the FHSA are products that are toxic, corrosive, irritants, flammable, combustible, or strong sensitizers.

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 flammability can be identified and measured using laboratory instruments. However, hazards such as toxicity, tissue corrosivity, eye irritancy, and skin irritancy result from the biological response of living tissue and organs to the presence of the hazardous substance. Since public policy prohibits experimental testing of these types of substances on human beings, other means must be relied upon to make these determinations. One alternative to the inappropriate testing of humans with hazardous substances is to test animals to determine the existence of the hazards addressed by the FHSA. In fact, the FHSA defines the hazard category of "highly toxic" in terms of animal toxicity when groups of ten or more rats are exposed to specified amounts of the substance. In addition, the Commission's regulations under FHSA concerning toxicity and irritancy utilize animal tests to determine the presence of the hazard being investigated.

However, 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



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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 has prepared this policy statement to state publicly its policy and procedures with respect to animal testing and to encourage the industries subject to the FHSA to follow a similar policy.

Therefore, in making the appropriate hazard determinations, the Commission and manufacturers of products subject to the FHSA, should whenever possible utilize existing alternatives to conducting animal testing. These include prior human experience, literature sources which record prior animal testing or limited human tests, and expert opinion. 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.

When the Commission does find it necessary to do animal testing to evaluate the hazard potential of a product, it uses the most humane procedures and fewest animals possible to get reliable results.

The Health Sciences Laboratory Division is responsible for providing sound data for evaluating product labeling as prescribed in the Federal Hazardous Substances Act and regulations. In achieving these goals, while also reducing the number of animals used in testing for reasons of humane treatment and reduction of expenses, the following procedures have been implemented:

- Acute toxicity, $LD_{50}$, is performed as a limit test. That is, the 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 to be non-toxic. 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.
- Eye irritancy testing is not performed if a product is known to be a primary skin irritant because experience has shown that products which are skin irritants are also eye irritants. When animal testing is the only feasible method of determining if a substance is an eye irritant, the animals are treated with two applications of tetracaine ophthalmic anesthetic, 10-15 minutes apart, prior to instilling the product to the eye, in order to reduce the pain and suffering of the animals tested. In addition, a tiered approach to testing, similar to that used for acute toxicity testing, is used to reduce the number of animals tested.
- Skin irritation testing has been modified from the original Draize test through elimination of the use of stocks for restraint during the exposure period. Currently, the animal's test sites are covered with a semi-occlusive patch and the animals are allowed free mobility and access to food and water. This has eliminated the previously encountered stress and dehydration experienced by use of stocks.



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The Health Sciences Laboratory has been monitoring ongoing research on non-animal test systems for prediction of toxicity and irritancy. When such techniques are accepted by the scientific community as adjuncts or alternatives to whole-animal testing, 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.

Dated: May 24, 1984.

Sadye E. Dunn,
Secretary, Consumer Product Safety Commission.

[FR Doc. 84-14374 Filed 5-29-84; 8:45 am)



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# TAB B. REGULATORY ANALYSIS



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

**Memorandum**

Date: September 19, 2011

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

The U.S. Consumer Product Safety Commission (CPSC) is considering amendments to *Hazardous Substances and Articles; Administration and Enforcement Regulations* under the Federal Hazardous Substances Act (FHSA). The amendments are intended to update 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.

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

Staff recommends changes to 16 CFR part 1500, *Hazardous Substances and Articles; Administration and Enforcement Regulations*. The suggested substantive changes, and staff's rationale for each change, are summarized below:

* This analysis was prepared by CPSC staff, and has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.



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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 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. 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 comprises 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 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



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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 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. 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 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[*] or the OECD Test Guideline 405: Acute Eye Irritation/Corrosion.[†]

[*] 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 )

[†] 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 )



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

The FHSA requires that the Commission provide a preliminary analysis of a proposed rule, including amendments to regulations promulgated under the FHSA, during development of the notice of proposed rulemaking. The preliminary analysis for staff's proposed amendments must contain "a preliminary description of the potential benefits and potential costs of the proposed regulation…" Additionally, 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 entities. Also, under the National Environmental Policy Act (NEPA), the Commission is required to consider the potential environmental effects of the proposed rule.

## Potential Benefits and Costs

Staff's suggested amendments would not materially affect the types and classes of products available for consumer use, nor would these amendments affect labeling of products to notify consumers of hazards associated with products. Consequently, the suggested amendments are not expected to result in benefits from reductions in the number of injuries or deaths. Similarly, the amendments suggested by staff are not expected to increase costs to manufacturers. For the most part, the changes are clarifications that make manufacturers aware of the Commission's animal testing policy. No additional testing or recordkeeping requirements are contemplated as a result of the proposed amendments. Because the amendments would bring greater attention to the availability of alternatives to animal testing, focusing on the reduction or replacement of animals in testing, any changes in costs are expected to be cost savings for manufacturers.

## Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) requires that the Commission consider whether a proposed 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 staff's suggested 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 suggested 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) recommended by CPSC staff 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 proposed rule. Staff's suggested amendments should not have



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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 proposed rule should not have adverse environmental consequences.



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# TAB C. PROPOSED STATEMENT OF POLICY ON ANIMAL TESTING



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**CPSC 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 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 animal testing may be necessary in some cases, 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), 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: <*web link here*>.

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

(1) Neither the FHSA nor the Commission's regulations *require* animal testing. Overall, in the cases where testing animals is necessary, 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



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approved by the Commission can be accessed via the Internet at: <*web link here*>. 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 the section, should refer to the Commission's animal testing Web page at: <*web link here*>.

*(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 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 website at: <*web link here*> 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* - 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 website 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 ($\leq 2$ or $\geq 11.5$) 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



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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 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* test data (identified on the Commission's animal testing website 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 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 <*web link here*>. 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



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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: <*web link here*>.



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