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

(A) 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.

(B) 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.

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

(A) When the weight-of-evidence is insufficient to determine a substance's ocular irritation, a Commission-approved *in vitro* or *in silico* assay for ocular irritancy should be run to assess eye irritation potential and determine labeling. Examples of Commission-validated *in vitro* assays are identified on the Commission's animal testing Web site at: *http://www.cpsc.gov/library/animaltesting.html*). If no valid *in vitro* test exists, the test strategy for determining dermal corrosion/irritation outlined in paragraph (b)(1)(ii)(B) of this section can be followed to determine ocular irritation.

(B) If the dermal test strategy outlined in section paragraph (b)(1)(ii)(B) of this section 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.

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

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

(2) [Reserved].

Dated: November 29, 2012.

Todd A. Stevenson,

Secretary, Consumer Product Safety Commission.

[FR Doc. 2012–29260 Filed 12–7–12; 8:45 am]

BILLING CODE 6355–01–P

CONSUMER PRODUCT SAFETY COMMISSION

[CPSC Docket No. CPSC–2012–0036]

16 CFR Part 1500

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

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

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

DATES: This rule is effective on January 9, 2013.

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

SUPPLEMENTARY INFORMATION:

A. Background

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

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

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

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

B. Response to Comments on the Proposed Rule

In the **Federal Register** of June 29, 2012, we published a proposed rule on revisions to the animal testing regulations (77 FR 38754). We received three comments on the proposed rule. Two of the comments were from individuals and the third comment was submitted jointly by the Alternatives Research and Development Foundation, American Anti-Vivisection Society, Humane Society of the United States, People for the Ethical Treatment of Animals, and the Physicians Committee for Responsible Medicine.

1. Non-animal Testing Alternatives

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

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

2. Alternatives

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

Response: The FHSA direct that reliable human experience data take precedence over differing results from animal tests. 15 U.S.C. 1261(h)(2). Therefore, the Commission would always consider human experience with products and substances first, when it exists, followed by a thorough examination of the existing animal database. The Commission likewise recommends this approach to manufacturers who are labeling substances to indicate a hazard. Accordingly, the proposed rule has been revised to make the preference for human data clearer in the regulatory text.

3. In Vivo Testing

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

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

Other Comments

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

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

C. Revisions to Animal Testing Regulations

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

Because there are other Commission-approved test methods that may be used

by CPSC staff or the public for toxicity testing and defining a substance as highly toxic, as reflected in the ICCVAM recommendations and outlined in the CPSC's statement of policy on animal testing published elsewhere in this **Federal Register**, the proposed rule added language (in underline) under new § 1500.3(c)(1)(iii) as follows: *A substance that produces a result of 'highly toxic' in any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.*

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

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

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

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

2. *Definition of toxic.* Currently, the test methods in § 1500.3(c)(2)(i)(A) through (C) used in the definitions of oral, inhalation, and dermal toxicity, respectively, each describe a method for defining a substance as *toxic.*

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

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

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

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

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

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

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

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

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

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

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

4. *Definition of irritant, primary irritant, and eye irritant.* Currently, 16 CFR 1500.3(c)(4) provides that the test methods for *irritant, primary irritant,* and *eye irritant* reference 16 CFR 1500.41 and 1500.42, which each describe a specific animal test method and outcome. For example, 16 CFR 1500.41 states that primary irritation to the skin is measured by a patch-test technique on the abraded and intact skin of the albino rabbit, clipped free of hair. A minimum of six subjects are used in the skin tests. To test for eye irritants, 16 CFR 1500.42 requires the use of six albino rabbits. Such tests require the test material be placed in one eye of each animal, while the other eye remains untreated, to serve as a control to assess the grade of ocular reaction.

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

The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results

in an empirical score of five or more when tested by the method described in 1500.41; *and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232. Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; *and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232.*

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

The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results in an empirical score of five or more when tested by the method described in § 1500.41; and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, *including data from in vitro or in silico test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data. Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, *including data from in vitro or in silico test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.*

5. *Method of Testing Toxic Substances*

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

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

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

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

6. *Method of Testing Primary Irritant Substances*

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

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

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

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

7. *Test for Eye Irritants*

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

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

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

Guidelines for *in vivo* and *in vitro* testing of ocular irritation of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis *or a validated in vitro test method* is recommended to evaluate existing

information before *in vivo* tests are considered. This analysis should include any of the following: existing human and animal data on ocular or dermal irritation, structure activity relationships, physicochemical properties, and chemical reactivity. *If in vivo* testing is *conducted,* a sequential testing strategy is recommended to reduce the number of test animals. Additionally, the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing is recommended. (a)(1) In the method of testing the ocular irritation of a substance referred to in § 1500.3(c)(4), six albino rabbits are used for each test substance* * *

8. *Editorial changes*

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

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

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

C. Impact on Small Businesses

The Commission certifies that this rule will not a have a significant impact on a substantial number of small entities under section 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 605(b). The Commission's Directorate for Economic Analysis prepared an assessment of the impact of amending the regulations on animal testing. That assessment found that there would be little or no effect on small businesses and other entities because the amendments will not result in product modifications in order to comply, and they will not result in additional testing or recordkeeping burdens.

D. Environmental Considerations

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

E. Executive Orders

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

F. Paperwork Reduction Act

This rule would not impose any information collection requirements. Accordingly, this rule is not subject to the Paperwork Reduction Act, 44 U.S.C. 3501–3520.

G. Effective Date

The Administrative Procedure Act generally requires that a substantive rule be published not less than 30 days before its effective date, unless the agency finds, for good cause shown, that a lesser time period is required. 5 U.S.C. 553(d)(3). The final rule will take effect 30 days after publication in the **Federal Register**.

List of Subjects in 16 CFR Part 1500

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

Accordingly, 16 CFR part 1500 is amended as follows:

PART 1500—[AMENDED]

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

Authority: 15 U.S.C. 1261–1278.

■ 2. Section1500.3 is amended by:
■ a. Revising paragraph (c)(1) introductory text;
■ b. Adding paragraph (c)(1)(iii);
■ c. Revising paragraph (c)(2) introductory text;
■ d. Revising paragraph (c)(2)(i) and
■ e. Revising paragraphs (c)(3) and (4).

The revisions and addition read as follows:

§ 1500.3 Definitions

* * * * *

(c) * * *

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

* * * * *

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

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

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

* * * * *

(3) Corrosive means a substance that causes visible destruction or irreversible alterations in the tissue at the site of contact. A test for a corrosive substance is whether, by human experience, such tissue destruction occurs at the site of application. A substance would be considered corrosive to the skin if a weight-of-evidence analysis suggests that it is corrosive, or validated *in vitro* test method suggests that it is corrosive, or if, when tested by the *in vivo* technique described in § 1500.41, the structure of the tissue at the site of contact is destroyed or changed irreversibly in 24 hours or less. Other appropriate tests should be applied when contact of the substance with

[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*)

other than skin tissue is being considered. A substance could also be labeled corrosive based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: Existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

(4) The definition of irritant in section 2(j) of the act (restated in paragraph (b)(8) of this section) is supplemented by the following: *Irritant* includes primary irritant to the skin, as well as substances irritant to the eye or to mucous membranes. *Primary irritant* means a substance that is not corrosive and that human experience data indicate is a primary irritant; and/or means a substance that results in an empirical score of five or more when tested by the method described in 1500.41; and/or a substance that can be considered a primary irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data. *Eye irritant* means a substance that human experience data indicate is an irritant to the eye; and/or means a substance for which a positive test is obtained when tested by the method described in 1500.42; and/or means a substance that can be considered an eye irritant based on the outcome of any of the approved test methods described in the CPSC's animal testing policy set forth in 16 CFR 1500.232, including data from *in vitro* or *in silico* test methods that the Commission has approved; or a validated weight-of-evidence analysis comprising all of the following that are available: existing human and animal data, structure activity relationships, physicochemical properties, and chemical reactivity data.

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

§ 1500.40 Method of testing toxic substances.

Guidelines for testing the toxicity of substances, including testing that does not require animals, are presented in the CPSC's animal testing policy set forth in 16 CFR 1500.232. A weight-of-evidence analysis, including any of the following: existing human and animal data, structure activity relationships, physicochemical properties; and chemical reactivity, or validated *in vitro* or *in silico* testing are recommended to evaluate existing information before *in vivo* tests are considered. If *in vivo* testing is conducted, a sequential testing strategy is recommended to reduce the number of test animals. The method of testing the toxic substances referred to in § 1500.3(c)(1)(ii)(C) and (c)(2)(iii) is as follows:

* * * * *

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

§ 1500.41 Method of testing primary irritant substances.

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

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■ 5. Amend § 1500.42 by adding introductory text, revising the first sentence of paragraph (a)(1), and revising paragraph (c) to read as follows:

§ 1500.42 Test for eye irritants.

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

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

* * * * *

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

Dated: November 29, 2012.

Todd A. Stevenson,

Secretary, U.S. Consumer Product Safety Commission.

[FR Doc. 2012–29258 Filed 12–7–12; 8:45 am]

BILLING CODE 6355–01–P

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

[CPSC Docket No. CPSC–2012–0005]

Requirements for Child-Resistant Packaging: Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The Consumer Product Safety Commission (CPSC, Commission, or we) is issuing a rule to require child-resistant (CR) packaging for any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline, a class of drugs that includes tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline, in a

[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*)