



[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

[Docket No. CPSC-2012-0037]

16 CFR Part 1500

Codification of Animal Testing Policy

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

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

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

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SUPPLEMENTARY INFORMATION:

A. Background

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

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

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

B. Response to Comments on the Proposed Policy

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

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

1. Alternative Test Methods

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

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

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

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

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

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

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

2. *In vivo* tests

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

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

3. Dermal Sensitization Test

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

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

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

4. Other Comments

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

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

List of Subjects in 16 CFR Part 1500

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

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

PART 1500 –[AMENDED]

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

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

2. Add § 1500.232 to read as follows:

§ 1500.232 Statement on animal testing policy.

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

(2) In order to determine the appropriate cautionary labeling, it is necessary to have objective criteria by which the existence of each hazard can be determined. Hazards such as toxicity, tissue corrosiveness, eye irritancy, and skin irritancy result from the biological response of living tissue and organs to the presence of the hazardous substance. One means of characterizing these hazards is to use animal testing as a proxy for the human reaction. In fact, the FHSA defines the hazard category of “highly toxic” in terms of animal toxicity when groups of 10 or more rats are exposed to specified amounts of the substance. The Commission’s regulations under the FHSA concerning toxicity and irritancy allow the use of animal tests to determine the presence of the hazard when human data or existing animal data are not available.

(3) Neither the FHSA nor the Commission’s regulations requires animal testing. The FHSA and its implementing regulations only require that a product be labeled to reflect the hazards associated with that product. If animal testing is conducted, Commission policy supports limiting such tests to a minimum number of animals and advocates measures that eliminate or reduce the pain or discomfort to animals that can be

associated with such tests. The Commission has prepared this statement of policy with respect to animal testing to encourage the manufacturers subject to the FHSA to follow a similar policy.

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

<http://www.cpsc.gov/library/animaltesting.html>. If a manufacturer or other entity performs a hazard test for FHSA labeling purposes that has not been previously approved by the Commission (*e.g.*, an ICCVAM-recommended test method or one of the tests described in the current version of the FHSA), CPSC staff will consider the data on a case-by-case basis and, upon review, determine whether to post the test method on the animal testing website.

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

(i) *Acute toxicity.* The traditional FHSA animal test for acute toxicity determines the median lethal dose (LD50) or lethal concentration (LC50), the dose or concentration that is expected to kill half the test animals. Procedures for determining the median LD50 /LC50 are described in section 2(h)(1) of the Act and supplemented in § 1500.3(c)(1) and (2) and the test method outlined in § 1500.40. The Commission recommends *in vitro* alternatives over *in vivo* LD50/LC50 tests, or using modifications of the traditional LD50/LC50 test during toxicity testing that reduce the number of animals

tested whenever possible. Data from *in vitro* or *in silico* test methods that have not been approved by the Commission may be submitted to the Commission for consideration of their acceptability. Commission-approved testing alternatives are identified on the website at: <http://www.cpsc.gov/library/animaltesting.html> and include:

- (A) *In vitro* and *in vivo* test methods that have been scientifically validated and approved for use in toxicity testing by the Commission;
- (B) Valid *in vitro* methods to estimate a starting dose for an acute *in vivo* test;
- (C) A sequential version of the traditional LD50 /LC50 tests described in § 1500.3(c)(1) and (2) and the test method described in § 1500.40, in which dose groups are run successively rather than simultaneously;
- (D) A limit-dose test where the LD50/LC50 is determined as a point estimate, which can still be used to categorize a hazard, although it gives no information on hazard dose-response. In the limit test, animals (10 rats) each receive a single dose of product at 5g per kilogram of body weight. If not more than one animal dies in 14 days, the product is considered to have an LD50 of greater than 5g/kg, and thus, deemed to be nontoxic. Only if two or more animals die is a second group of 10 rats tested (at a lower dose). This procedure reduces the number of animals tested from the 80 to 100 animals involved in a full LD50 test to, typically, 10 to 20 rats per product. This reduction in the number of animals tested is justified because an exact LD50 is not required by either the FHSA or the regulations. The FHSA requires only a categorical determination that the toxicity is greater than 5g/kg, between 50 mg/kg and 5g/kg, or less than 50 mg/kg.

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

(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 website at: <http://www.cpsc.gov/library/animaltesting.html>), the substance's dermal corrosivity/irritation (primary skin irritants and corrosives are also usually eye irritants and therefore do not need to be tested in the eye), evidence of ocular irritation of one or more structurally related substances or mixtures of such substances, data demonstrating high acidity or alkalinity of the substance, and any other relevant physicochemical properties that indicate the substance might be a dermal corrosive or irritant or ocular irritant.

(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 website at: <http://www.cpsc.gov/library/animaltesting.html>). If no valid *in vitro* test exists, the test strategy for determining dermal corrosion/irritation outlined in 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 website at: <http://www.cpsc.gov/library/animaltesting.html>), or weight-of-evidence analysis is recommended before *in vivo* animal sensitization testing is considered to determine

appropriate cautionary labeling. The weight-of-evidence analysis should incorporate any existing data on humans and animals, validated *in vitro* or *in silico* test results, and any relevant physicochemical properties that indicate the substance might be a dermal sensitizer. If there is any indication from this analysis that the substance is sensitizing to the skin, the substance should be labeled appropriately.

(2) [Reserved].

Dated: November 29, 2012

Todd A. Stevenson, Secretary
Consumer Product Safety Commission

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