Federal Register

Friday
October 9, 1992

Part II

Consumer Product Safety Commission

16 CFR Part 1500

Labeling Requirements for Art Materials Presenting Chronic Hazards; Guidelines for Determining Chronic Toxicity of Products Subject to the FHSA; Supplementary Definition of "Toxic" Under the Federal Hazardous Substances Act; Final Rules

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1500

Labeling Requirements for Art Materials Presenting Chronic Hazards; Guidelines for Determining Chronic Toxicity of Products Subject to the FHSA; Supplementary Definition of "Toxic" Under the Federal Hazardous Substances Act

AGENCY: Consumer Product Safety Commission.

ACTION: Final rules.

SUMMARY: This document announces three actions taken by the Consumer Product Safety Commission.[1] The Commission is finalizing the codification of ASTM standard D–4236 as a Commission rule which was mandated by the Labeling of Hazardous Art Materials Act ("LHAMA").

LHAMA also directed the Commission to issue guidelines specifying criteria for determining when any customary or reasonably foreseeable use of an art material can result in a chronic hazard. The Commission is issuing final chronic hazard guidelines as directed by LHAMA. Because the substance of the guidelines directed by LHAMA applies equally to materials other than art materials, these guidelines also may be used by the manufacturers of other products subject to the FHSA to determine whether their products present a chronic hazard and, therefore, require labeling under section 2(p) of the FHSA. The guidelines are not mandatory.

Finally, the Commission is issuing a final regulatory definition of toxic that will define chronic toxicity under the Federal Hazardous Substances Act (FHSA). This definition supplements the Commission's existing regulatory definition of toxic that concerns acute toxicity. The definition will apply to all products subject to the FHSA.

DATES: The codification of ASTM D–4236 (31500.14(b)(8)) which is effective on October 9, 1992.

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SUPPLEMENTARY INFORMATION:

[1] Copies of statements issued by each of the three Commissioners are available from the Office of the Secretary, Consumer Product Safety Commission, Washington, DC 20207; (301) 504–0800.

This document is effective on January 7, 1993.

I. Introduction

A. The Proposals

On April 17, 1991, the Commission proposed (1) a codification of ASTM D–4236 standard for labeling hazardous art materials as a Commission rule under the Labeling of Hazardous Art Materials Act ("LHAMA"); (2) guidelines for determining when an art material or other product subject to the FHSA may present a chronic health hazard; and (3) a supplemental regulatory definition of "toxic" (under the FHSA) to include chronic toxicity. 56 FR 15672 and 56 FR 15705 (1991). (The proposed guidelines and definition were together in one document.) The Commission proposed that the guidelines and the supplemental definition would apply to all products subject to the Federal Hazardous Substances Act ("FHSA").

The proposal originally provided for submission of comments until July 1, 1991. In response to numerous requests for more time to respond, the Commission extended the comment period to October 1, 1991.

LHAMA required the Commission to conduct a public hearing on guidelines issued under LHAMA. 15 U.S.C. 1277(d)(1). The Commission originally scheduled a hearing for July 18, 1991. However, when the period for written comments was extended, the Commission rescheduled the public hearing for October 17, 1991. The Commission has considered all written and oral comments on the three proposed actions.

This document summarizes the most significant public comments received and explains the Commission's responses to those comments. It attempts to clarify some points in the proposed actions that engendered confusion, and in doing so it addresses the major issues raised by comments. The preamble also explains the statutory bases for the Commission's actions and makes some changes in the proposals.

B. Overview of this Document

The Commission is finalizing three actions. Each is described in greater detail in a separate section of this preamble. First, the Commission is issuing the final codification of ASTM D–4236. LHAMA made this voluntary standard for labeling hazardous art materials a mandatory Commission rule under section 3(b) of the FHSA. Congress made some changes in provisions of ASTM D–4236, such as the definition of art material. Although LHAMA did not require the Commission to codify ASTM D–4236, the Commission decided to do so for the convenience of those subject to the LHAMA. Since the codification reflects changes by Congress, contains some editorial changes to make the standard consistent with other standards in the Code of Federal Regulations, and reflects the Commission's interpretation of the standard, the Commission determined to publish the codification as a proposed rule. 56 FR 15705. Today the Commission issues the codification in final form. The substance of the codification and the Commission's interpretation of certain provisions are explained in section III. of the preamble.

The second action taken by the Commission is the finalization of guidelines for determining chronic toxicity. LHAMA required the Commission to issue guidelines for determining when customary or reasonably foreseeable use of an art material can result in a chronic hazard. 15 U.S.C. 1277(d)(1). The guidelines proposed by the Commission on April 17, 1991, explained the principles used by the Commission staff in making this determination. The proposed guidelines specified conditions under which an art material would be considered to contain a carcinogen, neurotoxin, or a developmental or reproductive toxicant. The proposed guidelines also explained certain principles to be used in evaluating the risk resulting from exposure.

Because the principles behind the proposed guidelines apply to other products subject to the FHSA as well as to art materials, the Commission proposed that the guidelines could be used by manufacturers of all products subject to the FHSA to determine if the product presents a chronic hazard. As explained more fully in section II A. of this preamble, the FHSA requires that all products subject to that act must be properly labeled if they present a chronic hazard.

The Commission continues to believe that the principles behind the guidelines are applicable to all products subject to the FHSA. Thus, manufacturers of all such products may use the final guidelines to aid in their determination of whether their products present chronic health hazards. The Commission reiterates that the guidelines are not mandatory. Producers of art materials or any other product will not be required to follow the guidelines in determining chronic toxicity. However, as explained in section V.C. of the preamble, the Commission does expect that products subject to the FHSA will be appropriately labeled according to section 2(p) of the FHSA if they present a chronic hazard. The Commission may bring enforcement actions against such misbranded products.

Finally, the Commission is issuing a final rule under section 10 of the FHSA to supplement the current regulatory definition of "toxic." The existing

regulatory definition specifies tests to determine if a substance presents an acute toxic hazard but does not specify a similar means for defining a chronic toxicant. As explained more fully in section VII A. of this preamble, the statutory definition of "toxic" is quite broad and includes chronic as well as acute toxicity. The supplemental definition will close this gap between the statutory definition and the regulatory definition. As the definition is issued under the FHSA, it will apply to all products subject to the FHSA, not just art materials. As explained in section VII.B. of the preamble, the final definition is broader and more flexible than the one proposed.

II. Applicable Statutes

The Commission's actions are taken pursuant to two statutes: LHAMA and the FHSA. It is important to understand both statutes and how they work together.

A. The Federal Hazardous Substances Act

The FHSA, enacted in 1960, requires labeling of "hazardous substances" if they are "intended, or packaged in a form suitable, for use in the household or by children." 15 U.S.C. 1261(p). A hazardous substance that does not bear the labeling specified by section 2(p)(1) of the FHSA is misbranded and its introduction or receipt in interstate commerce is a prohibited act under the FHSA, 15 U.S.C. 1263, subjecting the violator to certain penalties, 15 U.S.C. 1264.

A hazardous substance under the FHSA includes "any substance or mixture of substances which (i) is toxic * * * if such substance or mixture of substances may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." 15 U.S.C. 1261(f)(1)(A). This definition encompasses two components: that the substance be "toxic" and that its reasonably foreseeable or customary use may cause substantial personal injury or illness.

The FHSA broadly defines the term "toxic" to apply to "any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface." 15 U.S.C. 1261(g).

The FHSA's labeling requirement for a hazardous substance (as defined in the act) that is intended or packaged for household use or for children is essentially self-executing. The FHSA does not establish a program of pre-marketing approval of products. Nor does it require the Commission to develop lists of hazardous substances. Rather, it is the manufacturers' responsibility to determine if their products are or contain a hazardous substance and must be labeled under the FHSA. Section 3(a)(1) of the FHSA does provide for the Commission to declare a particular substance to be a "hazardous substance" under the act in order to avoid or resolve uncertainty 15 U.S.C. 1262. But the Commission is not required to designate a substance as hazardous before enforcing the labeling requirements of section 2(p).

The Commission's regulations specify tests that can be used to determine whether a product presents a hazard of acute toxicity. 16 CFR 1500.3(c)(2). The existing regulations do not contain criteria to determine if a product presents a risk of chronic toxicity.

B. The Labeling of Hazardous Art Materials Act

The Labeling of Hazardous Art Materials Act (LHAMA), enacted November 18, 1988, amended the FHSA. 15 U.S.C. 1277. It provided that, as of November 18, 1990, the requirements for the labeling of art materials set forth in the 1988 version of ASTM D-4236 shall be deemed to be a Commission regulation issued under section 3(b) of the FHSA. Section 3(b) of the FHSA authorizes the Commission to issue labeling regulations different from or in addition to those of section 2(p)(1).

ASTM D-4236 requires producers and repackagers of art materials to submit the material's formulation to a board certified toxicologist for review. The toxicologist must determine whether the art material has the potential to produce a chronic health hazard and must recommend appropriate labeling. The requirements of ASTM D-4236 are explained in greater detail in section III. of this preamble.

LHAMA made some changes and additions to ASTM D-4236. LHAMA requires each producer or repackager of art materials to describe in writing the criteria used to determine whether the product has the potential to produce chronic adverse health effects. The producer or repackager must submit to the Commission those criteria and a list of the art materials that require chronic hazard warning labels. *Id.* sec. 1277(b)(3). Upon request of the Commission, the producer or repackager must also submit to the Commission the product formulations. *Id.* sec. 1277(b)(4).

In addition to the labeling required by ASTM D-4236, LHAMA provides that art materials that require chronic hazard labeling must include on the label the name and address of the producer or repackager, an appropriate telephone number, and a statement that the art materials are inappropriate for use by children. *Id.* sec. 1277(b)(5). LHAMA requires that 12 months after a producer or repackager has discovered significant information regarding hazards of the art material or ways to protect against the hazards, the new information must be incorporated into the chronic hazard label. *Id.* sec. 1277(b)(6).

LHAMA states that a toxicologist must "take into account opinions of various regulatory agencies and scientific bodies" in determining whether an art material has the potential to produce adverse chronic health effects. 15 U.S.C. 1277(b)(8). In a separate section, the statute requires the Commission to issue guidelines containing criteria for determining when "customary or reasonably foreseeable use of an art material can result in a chronic hazard." Congress directed the Commission to issue these guidelines within one year of enactment of LHAMA. *Id.* sec. 1277(d)(1). Due to the complexity of the scientific issues involved and the lack of a Commission quorum for a period of time, issuance of the guidelines was delayed.

III. Issues Concerning the Codification of D-4236

A. General Requirements

ASTM D-4236 requires the producer or repackager of an art material to submit the product's formulation to a toxicologist who will review the formulation to determine if the art material has the potential to produce chronic adverse health effects through customary or reasonably foreseeable use. The toxicologist will advise the producer or repackager of appropriate chronic hazard labeling and the producer or repackager must adopt suitable precautionary labeling. The labeling recommended must be in accordance with section 5 of ASTM D-4236. Such labeling includes a signal word, a list of potential chronic hazards, the name(s) of the chronically hazardous component(s), safe handling instructions, a list of sensitizing components, an identification of a source for additional health information, and, where appropriate, more detailed technical information in supplemental documents.

If the art material presents an acute hazard the labeling must also warn of it. Labeling of art materials subject to LHAMA must also conform to labeling

requirements of section 2(p) of the FHSA and regulations issued thereunder.

ASTM D–4236 states certain considerations that the reviewing toxicologist must "take into account." These include "opinions of various regulatory agencies and scientific bodies * * *on the potential for chronic adverse health effects of the various components of the formulation."

B. Statement of Conformance

ASTM D–4236 provides for a statement of conformance that informs the purchaser that the product complies to the standard. The standard specifies that the conformance statement "should appear whenever practical on the product," but it could also be placed on (1) the individual product package, (2) a display or sign at the point of purchase, (3) separate explanatory literature available on request at the point of purchase, or (4) a response to a formal request for bid or proposal.

The Commission interprets this provision of ASTM D–4236 to require that with every art material product there must be a conformance statement or, if it presents a chronic hazard, the product must have an appropriate precautionary label. Although the language of ASTM D–4236 does not clearly mandate a conformance statement for all art materials, the Commission believes that allowing use of conformance statements for some products but not others would result in confusion to purchasers. Purchasers would be in doubt whether an unmarked art material has been found not to present a chronic hazard or simply has not been reviewed at all. ASTM D–4236 expresses a preference that the conformance statement appear on the product, but the other options mentioned in the standard will also satisfy the conformance statement requirement.

C. Telephone Number

ASTM D–4236 requires that the precautionary label on an art material that has been determined to present a potential chronic health hazard must identify a source for additional health information. The ASTM D–4236 standard provides three examples of such a statement: (1) provision of a 24-hour toll free telephone number, (2) a statement to contact a physician, or (3) a statement to call the local poison control center.

The LHAMA requires, however, that "art materials that require chronic hazard labeling * * * must include on the label * * *, an appropriate telephone number." 15 U.S.C. 1277(b)(5). Thus, Congress has required that an actual telephone number appear on the label. The Commission believes that "an appropriate telephone number" is one which will enable the purchaser to obtain additional information about the product's potential chronic hazard. The number could be that of the producer or repackager or another source that could provide such information. However, the label must contain a phone number, not just a statement to contact a doctor, and it must be a United States telephone number.

D. Standard is Applicable only to Art Materials

The Commission emphasizes that the requirements of ASTM–D4236 as modified by LHAMA are applicable only to art materials. Thus, only producers and repackagers of art materials must submit product formulations to toxicologists to determine the product's chronic hazard potential and appropriate labeling. Non-art materials must be properly labeled under the FHSA if they are hazardous, but the FHSA does not impose any specific review procedure upon manufacturers of non-art materials. Rather it is the manufacturers' responsibility to determine by appropriate means whether their non-art material product is hazardous.

Congress provided a very broad definition of art material or art material product in LHAMA. The term is defined as "any substance marketed or represented by the producer or repackager as suitable for use in any phase of the creation of any work of visual or graphic art of any medium," excluding products subject to the Federal Insecticide, Fungicide, and Rodenticide Act or to the Federal Food, Drug, and Cosmetics Act. Although the Commission believes that the determination of what is or is not an art material must be made on a case by case basis, there are some general principles that the Commission believes will be helpful in enforcing the requirements for art materials.

The broad statutory definition could be interpreted to include many items not traditionally considered art materials, such as the many kinds of tools and implements used in the process of creating a work of art. The Commission does not believe that such a broad sweeping definition was intended by Congress. Statements during floor debates on the LHAMA amendment indicate a narrower interpretation. Examples noted are solvents in cements, permanent markers, and inks; lead in paints, clay, and glazes; cadmium in silver solders. 134 Cong. Rec. S16838 (Oct. 19, 1988) (statement of Sen. Gore). Similar examples also cited were solvents in oil painting and silk screening; solders for stained glass; lead in paints and ceramics; and asbestos in talcs and clays. *Id.* at S16838 (statement of Sen. McCain).

The Commission believes that under the statutory definition of "art material" three general categories can be discerned as follows:

1. Those products which actually become a component of the work of visual or graphic art, such as paint, canvas, inks, crayons, chalk, solder, brazing rods, flux, paper, clay, stone, thread, cloth, and photographic film.

2. Those products which are closely and intimately associated with the creation of the final work of art, such as brush cleaners, solvents, ceramic kilns, brushes, silk screens, molds or mold making material, and photo developing chemicals.

3. Those tools, implements, and furniture that are used in the process of the creation of a work of art, but do not become part of the work of art. Examples are drafting tables and chairs, easels, picture frames, canvas stretchers, potter's wheels, hammers, chisels, and air pumps for air brushes.

Although products falling in the third category could come within a broad interpretation of the term "art material," the Commission does not believe that Congress intended such a sweeping interpretation. Therefore, as a matter of enforcement policy, the Commission will not require that products falling in this third category comply with the standard for art materials. This means that the Commission will not require that formulations for such products be reviewed by a toxicologist. Manufacturers of such products would not be required by the Commission to submit their review criteria or lists of products requiring chronic hazard labels to CPSC. Nor do they have to provide a conformance statement for their products. However, the FHSA requires that all household or children's products (whether art materials or not) must be appropriately labeled if they are or contain a hazardous substance. 15 U.S.C. 1261(p). Thus, even a product that falls in the third category above must be appropriately labeled if it is toxic (acutely or chronically) and may cause serious injury or illness through reasonably foreseeable use.

This discussion is intended to provide some guidance on how the Commission interprets the statutory definition. Examples given are intended to illustrate the categories the Commission envisions. In making the determination of whether a product is an art material,

the Commission would consider the intended and anticipated uses of the product as indicated by, for example, its packaging and promotion. Firms that are uncertain whether their materials fall within the scope of this enforcement policy may request guidance from the Commission staff by addressing their inquiries to the compliance staff of the headquarters or the regional offices.

LHAMA made ASTM D–4236 a Commission regulation issued under section 3(b) of the FHSA. Section 3(b) authorizes the 'Commission to issue additional labeling requirements for "hazardous substance(s) intended, or packaged in a form suitable, for use in the household or by children." 15 U.S.C. 1262(b). When Congress enacted LHAMA it did not expand the Commission's authority under section 3(b) of the FHSA. Thus, there is a very narrow category of art material products, those that have no significant marketing except to schools for adults or to businesses for the use of adults away from the household, that are not subject to the FHSA. The Commission anticipates that very few products would fall within this category. The Commission's regulations at 16 CFR 1500.3(c)(10)(i) provide guidance on what types of products are considered to be intended, or packaged in a form suitable for use in the household. That regulation states in part: "the test shall be whether under any reasonably foreseeable condition of purchase, storage, or use the article may be found in or around a dwelling."

E. Board-Certified Toxicologist

ASTM D–4236 requires that art material formulations be reviewed by a toxicologist. It defines the term "toxicologist" as "any individual who through education, training, and experience has expertise in the field of toxicology, as it relates to human exposure, and is either a toxicologist or a physician certified by a nationally recognized certification board."

LHAMA did not alter this requirement of review or the definition of toxicologist. Several commenters expressed concern that allowing only board-certified toxicologists and physicians is too limited and that many toxicologists who are not certified would also be capable of making the determinations required under ASTM D–4236. However, this requirement of board certification is part of the standard made mandatory by LHAMA. LHAMA provides for the Commission to amend the standard if it follows certain procedures. The Commission cannot abolish the requirement of board certification without following these procedures. However, in enforcing LHAMA the Commission is primarily concerned that the person reviewing formulations has sufficient knowledge based on a combination of education, training, and experience and that the reviewer uses appropriate criteria to recommend complete and accurate labeling. Any enforcement action would be based on the failure to conduct an adequate product review resulting in noncomplying cautionary labeling, rather than on the fact that a toxicologist is not certified. As a matter of enforcement policy, the Commission will not require that all art material reviews be done by a board-certified toxicologist. When the Commission considers rulemaking to amend the codified ASTM standard, it will consider deleting the requirement of board certification.

F. Amendment of ASTM D–4236

Congress provided that the Commission can revise the standard LHAMA mandated if the Commission determines that the standard is "inadequate for the protection of the public interest" and that the Commission's amendment will adequately protect the public interest. The amendment must be issued in accordance with the procedures of section 553 of the Administrative Procedure Act allowing an opportunity for notice and comment. In addition, the Commission must allow interested persons an opportunity to present oral comments.

If ASTM proposes a revision to D–4236, LHAMA provides that the Commission shall incorporate it if the Commission determines that the revision is in the public interest. The Commission must provide for notice and comment concerning the revision. 15 U.S.C. 1277(c).

G. Annexes and Appendix

ASTM D–4236 contained two annexes and one appendix. One of the annexes provides chronic hazard statements. Section 5.2 of ASTM D–4236 (§ 1500.14(b)(8)(i)(E)(*2*) in the codification) states that potentially chronic hazards must be stated "substantially in accordance with statements" in the first annex. The second annex provides precautionary statements. Section 5.4 (§ 1500.14(b)(8)(i)(E)(*4*) in the codification) states that "appropriate precautionary statements as to work practices, personal protection, and ventilation requirements shall be used substantially conforming to those" in the second annex. These annexes are §§ 1500.14(b)(8)(i) (F) and (G) in the codification below.

The Commission considers the chronic hazard statements and the precautionary statements to be examples of appropriate statements when a product presents a chronic hazard. The Commission considers these lists to be suggestive, and does not consider these to be the only statements of hazard or precaution that could be used.

Because products other than art materials that are subject to the FHSA may present similar chronic hazards, manufacturers of non-art materials may find these lists of chronic hazard statements and precautionary statements helpful in labeling their products under section 2(p) of the FHSA. All products subject to the FHSA must be appropriately labeled for any acute hazards they present.

In addition, the staff is in the process of updating its 1979 labeling guide for products that present an acute hazard. The updated version would include recommendations on designing warning labels and examples of warning statements for products that pose a chronic hazard. This labeling guide would be appropriate for all products subject to the FHSA.

ASTM D–4236 also contained an appendix which provided guidelines for organizations that certify an art material conforms to the requirements of ASTM D–4236. In the proposed codification published on April 17, this appendix was erroneously listed as § 1500.14(b)(8)(i)(H) of the codified standard rather than as an appendix. The final codification corrects this and clarifies that these guidelines are not mandatory.

IV. Issues Concerning the Chronic Hazard Guidelines

A. Broad Scope

LHAMA requires the Commission to issue guidelines for determining when an art material presents a chronic hazard. When the Commission published proposed guidelines, it stated that the guidelines could be used for non-art materials as well because the basic principles behind the guidelines would apply broadly to all products subject to the FHSA. Although the Commission received several comments concerning the scope of the guidelines, the Commission is maintaining the broad scope of the proposed guidelines.

Essential to understanding this view is the fact that the guidelines are not mandatory. The Commission's purpose in issuing these guidelines is not to

create a static classification system that must be followed by manufacturers. Rather, the FHSA makes it the manufacturers' responsibility to properly label their products. The guidelines are intended to help the manufacturer in making that determination. The process set out in the guidelines would not be affected by the classification of a product as an art material or other product subject to the FHSA. The scientific principles upon which the guidelines are based are the same. It makes sense then, that the guidance available for art materials would also be useful for non-art materials. (The codification of ASTM D-4236, however, applies only to art materials. Thus, only manufacturers and repackagers of art materials must submit their products' formulation to a toxicologist and must supply the Commission with their criteria for determining chronic toxicity and a list of art materials that require chronic hazard labeling.)

The Commission has authority to issue these guidelines under the FHSA as part of its ability to regulate hazardous substances under that statute. As discussed in section VII.A. of the preamble, the FHSA provides the Commission with clear authority over household and children's products that present a chronic hazard. Section 2(p) of the FHSA requires appropriate labeling of hazardous substances, chronic as well as acute. It is within the Commission's general authority under the FHSA to provide guidance to manufacturers on determining whether a product presents such a hazard and therefore must be labeled. By issuing the guidelines the Commission is not imposing new requirements beyond those already made by section 2(p) of the FHSA.

B. Complexity of Determination

The Commission recognizes that determining if a product presents a chronic hazard is highly complex and often relies upon incomplete or non-conclusive data. The determination requires the exercise of professional judgment.

Under the FHSA, for a substance to be a "hazardous substance" (and thus require labeling) it must have the potential both to be toxic *and* to "cause substantial personal injury or illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." The fact that a product contains a toxic substance does not make the product a "hazardous substance" under the FHSA. The second component of the definition must be considered. For instance, the manufacturer must account for the amount of the substance in the product, for the bioavailability of the substance, and for exposure to the substance. This second aspect of the definition makes the determination of the need for labeling a complex decision.

C. Customary or Reasonably Foreseeable Handling or Use

Some comments expressed concern that the Commission had not provided sufficient guidance on the meaning of the phrase "customary or reasonably foreseeable handling or use" that is part of the definition of "hazardous substance" in the FHSA. The precise meaning of the phrase will, of course, depend on the product at issue. However, the Commission's regulations at 16 CFR 1500.3(c)(7)(iv) provide some general guidance and state:

> Reasonably foreseeable handling or use includes the reasonably foreseeable accidental handling or use, not only by the purchaser or intended user of the product, but by all others in a household, especially children.

Thus, in general, the Commission has taken a fairly broad view of what is reasonably foreseeable handling or use.

As far as the guidelines are concerned, defining a reasonable use scenario can be the most uncertain part of exposure assessment. As the guidelines indicate, there are many variables to consider. Exposure assessment is a mixture of science, knowledge of the product under consideration, and common sense. Unfortunately, due to the large number of art materials and other household and children's products, it is impossible to specify typical scenarios for all cases. Nevertheless, scientists have conducted exposure and risk assessments for many products.

D. Guidelines Do Not Require Submission of Data

The guidelines are intended as an aid to manufacturers in making their determination of whether a product is a hazardous substance due to chronic toxicity and thus would require labeling under the FHSA. The guidelines themselves establish no mandatory requirements.

LHAMA and the modified version of ASTM D-4236 mandated by that law do place certain requirements upon the manufacturers and repackagers of art materials. Thus, only the formulations of art materials must be submitted to a toxicologist for review. For other products, as has always been the case under the FHSA, it is up to the manufacturer to determine proper labeling. The FHSA does not establish a required procedure for doing this. The guidelines do not change this arrangement, but they provide guidance for making that determination.

E. Risk Assessment for Children's Products

For the reasons explained below, the Commission has decided not to include additional safety factors for children's products in the final guidelines and definition. As with other scientific issues of this type, support exists both for applying an additional safety factor of ten for children's products and for not doing so. For example, a child might be more sensitive than an adult in the case of lead poisoning, while adults may be more sensitive than children in the case of neurotoxicity of certain pesticides.

Since, on the basis of much of the theory and data, it was very possible that children would be more susceptible to many substances, the additional factors of ten were proposed to provide an extra margin of safety for children. After reviewing the comments relating to this issue and considering how the additional protective levels would be implemented, the Commission has decided not to include these additional safety factors for children's products. A more detailed response to these comments and a discussion of the analysis followed by the Art & Craft Materials Institute ("ACMI") compared with that recommended in the guidelines is contained in the comment section of the preamble, section VIII.

As a result of analysis of the comments, several overall themes have become clear. First, CPSC's proposed methods of calculating the allowable daily intake ("ADI") for adults are similar, or result in a lower allowable risk, to those allowed by other agencies for both children and adults. Second, ACMI's conclusion that the labeling status of many art materials would be affected is not consistent with the intended use of CPSC's guidelines, since it appears that in many cases, ACMI has applied redundant safety factors in its exposure assessments which result in the overestimation of risk. Third, the ten-fold factor for children, if applied as the staff intended and without redundant safety factors, would have minimal economic impact.

However, there are difficulties in determining if a product that poses a chronic hazard would be used by children. Because many factors would have to be considered, determination of whether children would use these materials would have to be made on a

case-by-case basis. Factors that would be considered include the appeal of the product in attracting and sustaining use; ability of a child to use the product; ability to appreciate the product; adult's perception of intended use, marketing, packaging, advertising, and promotion of the product; and the manufacturer's stated intent. In many cases, it may be impossible to conclude that a given product would not be used by children. Thus, most products could be subject to the additional factor of ten for children. A net effect of requiring labeling for all products exceeding a cancer risk of 1×10^{-7}, for example, was not the intent of the proposed guidelines. Thus, the final guidelines do not provide additional safety factors for children's products.

F. Legal Effect of Guidelines

The guidelines are not issued as substantive binding rules, but are a non-mandatory statement of Commission policy. They explain how the Commission determines whether a product presents a chronic hazard, and they provide guidance to those in industry whose responsibility it is to determine if their product is properly labeled under the FHSA. Some minor changes have been made in the final guidelines to clarify their non-mandatory nature.

LHAMA required the Commission to issue chronic hazard guidelines for art materials. Congress directed the Commission to develop guidelines, not a binding rule that would automatically categorize all art materials. Thus, the guidelines set forth recommended procedures to be followed with the use of expert judgment rather than mechanically. As explained elsewhere, the Commission believes that these guidelines will also be helpful to the manufacturers of non-art materials subject to the FHSA.

V. Issues Pertinent to All Three Actions

A. Preemption

The Commission received numerous comments concerning the issue of preemption of state laws and regulations.

Section 18(b)(1)(A) of the FHSA provides generally that:

> If a hazardous substance or its packaging is subject to a cautionary labeling requirement under section 2(p) or 3(b) designed to protect against a risk of illness or injury associated with the substance, no State or political subdivision of a State may establish or continue in effect a cautionary labeling requirement applicable to such substance or packaging and designed to protect against the same risk of illness or injury unless such cautionary labeling requirement is identical to the labeling requirement under section 2(p) or 3(b).

15 U.S.C. 1261n.

LHAMA mandated ASTM D–4236, with certain modifications, as a Commission rule under section 3(b) of the FHSA. Since LHAMA amended the FHSA, the FHSA's preemption provision applies. Thus, this standard for labeling of art materials, as a 3(b) rule, preempts non-identical state and local labeling requirements that are designed to protect against the same risk of illness or injury as ASTM D–4236, as modified by LHAMA.

LHAMA directed the Commission to issue chronic hazard guidelines. The guidelines finalized today are issued pursuant to that provision of LHAMA and the Commission's general authority under the FHSA. As explained above, the standard ASTM D–4236 as mandated by LHAMA has preemptive effect if the other conditions of FHSA section 18(b)(1)(A) are met. The guidelines, however, are not a labeling requirement. They do not require that any particular product be labeled. The requirement that hazardous substances be labeled appropriately comes from section 2(p), not the guidelines. The guidelines are a non-mandatory guide for determining whether a product presents a chronic hazard. Thus, the guidelines themselves do not have a direct preemptive effect. As may affect labeling for chronic hazards, however, they may have an indirect preemptive impact because the labeling requirement of section 2(p) could preempt different state or local requirements.

The supplemental definition of "toxic" is not itself "a cautionary labeling requirement" and would not, in itself, preempt a state or local definition of "toxic." However, the supplemental definition defines a term that is necessary to the labeling requirements of section 2(p) and section 3(b) just as the existing regulatory definition of toxic, which applies to acute toxicity, works together with the labeling requirement. For example, while a different state definition of "toxic" might not be preempted automatically, a state labeling requirement that exempts from labeling a hazardous substance that is hazardous because of the risk of chronic toxicity (as defined by the supplemental regulatory definition) could be preempted.

B. The CHAP Process

Another comment raised frequently concerned the appropriateness of convening a Chronic Hazard Advisory Panel ("CHAP") to develop or evaluate chronic hazard guidelines. As most commenters seemed to recognize, neither the FHSA nor LHAMA requires the Commission to convene a CHAP before issuing chronic hazard guidelines. The Commission must establish a CHAP before initiating rulemaking to ban a substance under section 2(q)(1) of the FHSA relating to the risk of cancer, birth defects, or gene mutations from a consumer product. 15 U.S.C. 2080(b)(1). The CHAP must submit a report to the Commission concerning whether a substance in the product is a carcinogen, mutagen, or teratogen. *Id.* Thus, the only action under the FHSA that requires the Commission to consult a CHAP is rulemaking to ban a particular substance.

In issuing these guidelines, however, the Commission is not promulgating a binding rule, is not seeking to ban a substance, and is not taking action with respect to any particular substance. Issuance of these guidelines is not appropriate for CHAP review. The CHAP's purpose is to review particular products and advise the Commission on the chronic risk posed by that product or by specific substances contained in the product. The chronic hazard guidelines being issued do not relate to any particular products or substances, but they provide guidance for determining, in general, whether a product can present a chronic health hazard.

The Commission certainly agrees that the guidelines should reflect sound scientific judgment and should be widely reviewed and commented upon. Other Federal agencies and interagency groups have reviewed relevant parts of the guidelines at CPSC staff's request prior to their publication for public comment, to ensure that the latest science has been addressed. The Commission published proposed guidelines and sought written comments even though LHAMA did not require the Commission to do so. The Commission also received comments as a result of the public hearing held in October. The Commission does not believe, however, that the CHAP process is the most appropriate means to obtain views on the guidelines.

CPSC staff is involved in many government and nongovernment activities to ensure consistency, use of the latest data, and use of the most current scientific approaches to the risk assessment process. These groups include the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET), the International Life Sciences Institute (ILSI), and the National Academy of Sciences (NAS) Committee on Risk Assessment Methodology (CRAM) processes. CPSC staff is also involved with a number of

interagency committees such as the Interagency Pharmacokinetics Group and the Interagency Committee on Neurotoxicity (which, at CPSC's request, reviewed the neurotoxicity guidelines before they were proposed). Participating in these efforts, the consideration of the comments received by expert scientists, and the fact that there are very few departures in the guidelines from generally accepted risk assessment methodology, lends credence to the assertion that the guidelines are scientifically defensible and reasonable.

C. Enforcement

The Commission emphasizes that there has not been, nor will there be, enforcement of the guidelines as such. Even once the guidelines become final they will not be treated as mandatory requirements which must be followed by manufacturers. A firm could follow a different but sound and scientifically supportable analysis to determine whether a product presents a chronic hazard.

However, the Commission has enforced, and will continue to enforce, the FHSA requirements that a household product that is or contains a hazardous substance must be appropriately labeled to advise of the hazard. In addition, the Commission has sought to enforce the specific, and largely procedural, requirements that LHAMA mandated for art materials. During 1991, the Commission staff contacted all known manufacturers and repackagers of art materials to advise them of the procedural requirements of LHAMA which went into effect on November 18, 1990. In 1992, inspections are being made of firms that have not given some indication of compliance or if there is some other reason to suspect noncompliance. When firms are found with products or practices that are not in compliance, they will normally be given the opportunity to voluntarily make the necessary corrections. Only when a firm has demonstrated a refusal to cooperate voluntarily would legal action be sought to obtain compliance.

VI. The Chronic Hazard Guidelines

A. General

1. Toxicity and Exposure

As explained earlier, the definition of "hazardous substance" requires both that the substance fall into one of the designated hazard categories, in this case that of "toxic," and that the substance "may cause substantial personal injury or illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." Any of the chronic hazards, including but not limited to cancer, neurotoxicity, or developmental or reproductive toxicity addressed by this notice constitute "substantial personal injury or illness." In order to determine whether a product should be regarded as a hazardous substance, one must determine not only that the product has the potential to be toxic, but that in any customary or reasonably foreseeable handling or use persons are exposed to the toxic component(s) in a way that presents a significant risk of the substantial adverse health effect potentially associated with the product. This latter factor can be considered to reflect the person's exposure to the toxic component or the bioavailability of the component.

2. Nature of the Guidelines

Except as specifically noted, the current scientific knowledge concerning chronic hazards is insufficient to allow the guidelines to specify criteria that can be mechanically applied to determine whether a product is toxic. Interpretation of certain points in the guidelines will likely require expert knowledge and the application of professional judgment. Thus, the guidelines do not present a simple blueprint into which a given set of facts may be inserted to receive a certain determination. Rather, careful expert judgment must be used. If questions arise concerning matters not clarified by these guidelines, guidance may be obtained from previous Commission toxicity, exposure, and risk assessments; or from the Commission's Directorate for Health Sciences.

These guidelines contain a number of assumptions, methodologies, and procedures for determining chronic hazard and risk. While these are currently the most scientifically justified choices in the opinion of the Commission, the Commission recognizes that new data and methodologies continue to be developed. Accordingly, all default assumptions (i.e., numerical factors to be used in the absence of data for the particular substance or circumstance) contained in the following sections on hazard and risk determination may be replaced as new data become available.

In determining whether a substance should be regarded as hazardous all available scientific evidence should be considered. However, the guidelines do not require any additional laboratory tests to determine toxicity or exposure.

A condensed version of the guidelines will appear at 16 CFR 1500.135. A supplemental definition of "toxic" that defines chronic toxicity will appear at 16 CFR 1500.3(c)(2)(ii). The guidelines summarize discussions contained in documents prepared by the Commission's Directorate for Health Sciences. This preamble is also drawn from the backup documents and is intended to aid in interpretation of the guidelines. Copies of the backup documents are available at the Commission's Office of the Secretary, Consumer Product Safety Commission, room 428, 5401 Westbard Avenue, Bethesda, Maryland.

B. Carcinogenicity

1. Introduction

This section discusses the chronic hazard guidelines concerning carcinogenicity. The guidelines for determining chronic hazards by reason of carcinogenicity are especially needed because of (1) the long latency period between the initial exposure to a carcinogen and the appearance of tumors, (2) the fact that humans are exposed to multiple carcinogenic agents during the latency period under generally uncontrolled conditions (and other factors discussed below), and (3) the controversies that have surrounded the conditions under which tests showing a carcinogenic response in animals should be considered relevant to human risk. These factors make it impossible to demonstrate conclusively that such substances are human carcinogens. Nevertheless, considerable agreement exists in the scientific community as to the nature and amount of evidence that should exist in order to conclude that a substance is a likely human carcinogen.

The intent of the guidelines is to incorporate those areas where there is a substantial consensus as to the evidence needed to support a conclusion that a substance is a likely human carcinogen. For substances where the available evidence does not meet this standard, or where there is controversy about how the evidence should be evaluated, the Commission may proceed by rulemaking, as provided in section 3(a) of the FHSA, or by enforcement actions on a case-by-case basis to resolve the question of whether the substance presents sufficient evidence of an ability to be carcinogenic in humans that the substance should be considered toxic.

Evidence for carcinogenicity largely comes from two sources: Human studies (epidemiology) and animal studies (long-term carcinogen bioassay). Epidemiology is a broad medical science that deals with the incidence,

distribution, and control of disease in a population. Results from these epidemiologic and animal studies are supplemented with available information from short-term tests, pharmacokinetics (absorption, distribution, metabolism, and elimination of substances), and other relevant toxicological data. The guidelines would evaluate the toxicity of a substance on the basis of potential carcinogenicity by evaluating the available human and animal data. Under the guidelines, substances for which "sufficient evidence" exists to demonstrate carcinogenicity from studies in humans would be considered to be toxic. In addition, those substances for which there is "limited evidence" of carcinogenicity in humans or "sufficient evidence" of carcinogenicity in animals are considered toxic, except that evidence derived from animal studies that has been shown not to be relevant to humans is not included.

As noted above, it will be necessary to continue to rely on rulemaking under section 3(a) of the FHSA, or on enforcement actions, to resolve uncertainties that are not addressed by these guidelines. In this regard, the Commission is aware that the criteria stated in the guidelines do not lend themselves to a mechanical application. A number of the criteria include statements that themselves can be applied to particular chemicals only by the exercise of expert technical judgment. For example, one of the factors stated below for determining that an epidemiological study shows a causal relationship between exposure to an agent and cancer is that all possible confounding factors which could account for the observed association are eliminated after consideration. Expert technical judgment is required to identify possible confounding factors and to evaluate whether the available data are adequate to eliminate the factors as causes of the observed association. In some instances, this determination will not be straightforward. In these cases, the guidelines will not resolve the controversy, and it may be appropriate for the Commission to conduct rulemaking to resolve the controversy, or to bring enforcement actions in which the toxicity of the substance would be established on a case-by-case basis.

Although there are many difficult issues related to the interpretation of cancer studies in animals and humans, criteria for defining carcinogenicity have been established by several groups, such as the International Agency for Research on Cancer (IARC), the American National Standards Institute (ANSI), and the U.S. Environmental Protection Agency (EPA)

The following discussion explains the scientific principles and evidentiary approach upon which a determination that a substance is a "sufficient evidence" human or animal carcinogen or a "limited human evidence" carcinogen would be based. The criteria that are commonly used to evaluate the evidence derived from human and animal carcinogenesis data outlined in the following sections are similar to those of IARC and EPA, except for a few differences that are explained below.

2. Assessment of Evidence for Carcinogenicity from Studies in Humans.

a. *Discussion.* Epidemiological studies are the only direct means of assessing carcinogenicity of a substance in humans (the Office of Science Technology Assessment and Policy (OSTP), 1985, Principle # 15). Epidemiologic data are obtained from occupational, therapeutic or consumer exposure to a substance. These studies can provide sufficient evidence for a causal hypothesis (such as that between cigarette smoking and lung cancer) and compelling reasons for prevention of a health hazard (OSTP, 1985, p. 10421). They examine both the distribution of a disease using descriptive studies (correlational approaches) and determinants of a disease using analytical studies (case control and cohort methods) (OSTP, 1985, Principles ##16 & 17, p. 10377).

A good quality epidemiological study should have a clear and detailed description of the study population, disease, and exposure. The design of the study should have dealt with bias and confounding factors that can influence the risk of disease by matching, or the analysis should have dealt with bias and confounding factors by statistical adjustments (IARC, 1987, Suppl. 7, p. 26). The study should describe the determination of statistical parameters, such as relative risk, odds ratio, absolute disease rate, confidence intervals, significance tests, and adjustments made for confounding factors. The study should also describe the selection and characterization of exposed and control population, the adequacy of duration, the quality of follow up, and the identification of bias and confounding factors. A causal relationship is strengthened by the observation of a dose-response relationship, the consistency and reproducibility of results, the strength and specificity of the association, the mechanism of action, and other considerations (OSTP, 1985, p. 10421).

In assessing the strength of epidemiological studies, it is necessary to take into account the possible role of bias, confounding factors, and chance (IARC, 1987, Suppl. 7, p. 26; OSTP, 1985, Principle #18, p. 10377). "Bias" means that the operation of certain factors in the design and execution of a study lead erroneously to a stronger or weaker association between an agent and the disease than in fact exists. Confounding factors are factors associated with a test agent which create a situation in which the relationship between the test agent and a disease is made to appear stronger or weaker than it truly is as a result of the association between the confounding agent(s) and the test agent. Chance relates to the statistical significance of the observed causal association between the exposure to the agent and the development of the disease. This is ascertained by proper statistical analysis of the data. The statistical power of a study depends upon the size of the study group, the number of subjects exposed, and the level of excess risk which is required to be detected (OSTP, 1985, p. 10423).

The common problems encountered in epidemiological studies involving chemicals are: Long latent periods that exist between exposure to a carcinogenic agent and the development of cancer; inability to control for confounding risk factors; exposures to mixtures of chemicals; frequent absence of appropriate groups from the study; and difficulty in obtaining accurate and unbiased historical exposure assessment, disease ascertainment, and direct detection of relatively low level cancer risk (OSTP, 1985, p. 10424). These studies are inherently capable of detecting only comparatively large increases in the relative risk of cancer. Negative results even from high quality epidemiological studies cannot prove the absence of an association between the carcinogenic effect and the exposure (OSTP, 1985, Principle # 19, p. 10377). However, a well-designed and conducted epidemiological study with well-defined and usable exposure data can be used to assess upper limits of risk. Such a study is especially useful in this regard if there is animal evidence from well-conducted studies to show that the agent is potentially carcinogenic in humans (EPA, 1986, p. 33996).

The criteria stated below for assessing the evidence of carcinogenicity derived from human studies agree with those outlined by EPA, except that the "No Data Available" and the "No Evidence of

Carcinogenicity" classifications are deleted because they are not necessary for the purpose of determining toxicity. The criteria also agree with those of IARC, except that the "Evidence Suggesting Lack of Carcinogenicity" classification is deleted for the same reason, and the criteria suggested below include life-threatening benign tumors in the evaluation of human studies for the purpose of protecting public health. In this regard, the Commission agrees with EPA's position on benign tumors, because the threat to life is the most important consideration in health risk evaluations. Benign tumors could be life threatening if they are critically located, such as brain tumors (gliomas), which can compress and destroy the surrounding brain tissue, or tumors located in endocrine glands (hormone producing glands, like the pancreas, or pituitary), which can cause an imbalance of critical hormones.

The American National Standards Institute (ANSI, Z129.1–1988) did not specify criteria for the evidence of carcinogenicity derived from epidemiological studies but made use of epidemiological data in its overall categorization of carcinogens.

A causal relationship between exposure to an agent and cancer is established if one or more epidemiological investigations that meet the following criteria show an association between cancer and exposure to the agent: (1) No identified bias that can account for the observed association has been found on evaluation of the evidence, (2) all possible confounding factors which could account for the observed association can be ruled out with reasonable confidence, and (3) based on statistical analysis, the association has been shown unlikely to be due to chance.

b. *Categories of human evidence.* The following categories of evidence from human studies have been developed.

i. Sufficient evidence of carcinogenicity in humans. The evidence is considered sufficient when all three of the above criteria for establishing a causal relationship between exposure to the agent and development of cancer are fully met. Evidence in this category would establish that a substance is toxic.

ii. Limited evidence of carcinogenicity in humans. The evidence is considered limited for establishing a causal relationship between exposure to the agent and cancer when a causal interpretation is credible, but chance, bias, or other confounding factors could not be ruled out with reasonable confidence. Evidence in this category would establish that a substance is toxic.

iii. Inadequate evidence of carcinogenicity in humans. The evidence is considered inadequate when all of the above three criteria for establishing a causal relationship between exposure to the agent and cancer are not met, leaving an alternative explanation to be equally likely. Evidence in this category is insufficient to establish that a substance is toxic, but does not imply that non-carcinogenicity has been proven.

3. Assessment of Evidence for Carcinogenicity in Animals

a. *Relevance of animal data to humans.* In the absence of adequate human data, the next best source of evidence of the carcinogenicity of chemicals is animal data, which are considered relevant to humans for the following reasons. (1) Mechanistically, an induction of heritable changes in the cellular DNA is generally considered to be the first and major event in carcinogenesis, and DNA is chemically similar in humans and animals. (2) Several agents, *e.g.*, 4-aminobiphenyl, bis (chloromethyl) ether, diethylstilbestrol, melphalan, methoxalen plus ultraviolet radiation, mustard gas and vinyl chloride were first found to be carcinogenic in animal studies before they were found to be carcinogenic in human studies (IARC, 1987, Suppl. 7, p. 22). (3) Information evaluated by IARC shows that, out of the 44 agents for which there is "sufficient" or "limited" evidence of carcinogenicity to humans available, all 37 agents that have been tested adequately were found to produce cancer in at least one animal species. Based on this observation, IARC stated: "Although this association can not establish that all agents that cause cancer in experimental animals also cause cancer in humans, nevertheless, in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence (see p. 30) of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans." (IARC, 1987 Suppl. 7, pp. 22 & 30).

b. *Factors in the consideration of animal data.* Animal studies to determine the carcinogenicity of an agent involve both exposure of laboratory animals to the agent for a long period of time (several months to the entire life span) and histopathologic examination of the animals at the end of the study to detect an exposure-related increase in tumor incidence. Criteria for assessing the quality and adequacy of animal studies have been discussed by various groups (OSTP, 1985; National Toxicology Program (NTP), 1984). A good animal study (carcinogen bioassay) requires consideration of a variety of factors. For example: (1) The species and strain of animals used in the study should have a sufficient historical data base; (2) animals should be disease free and kept under good housing conditions and animal care; (3) the number of animals/group/sex should be adequate; generally 50 or more animals of each sex/group should be used; (4) animals should be randomly distributed in the groups; (5) dose levels selected should be adequate; at least one of the doses should be close to the maximum tolerated dose (MTD); doses in excess of the MTD may lead to increased mortality excessive toxicity, or other unphysiologic conditions not considered desirable in a carcinogen bioassay (OSTP, 1985, p. 10413, Principle #4, p. 10376); and (6) exposure duration and frequency should be adequate (daily exposure by oral or inhalation routes for a two-year period is generally used in rodents) (NTP, 1984).

Other factors associated with a good animal cancer bioassay or study that must be considered in assessing the evidence are: (1) Whether data collection and reporting are complete and clear, (2) whether routes, exposure patterns, and possible mechanisms of cancer induction are relevant to the human situation, *e.g.*, tumor development only at the site of transplant or injection of a material, or bladder tumors in the presence of bladder stones (OSTP, 1985, p. 10414; Principle # 4, p. 10376), (3) whether metabolic-pharmacokinetic properties are affected, and whether pathways required for activation of the agent to produce cancer are lacking in humans; if humans do not have the same metabolic pathway found necessary in the test animal for the carcinogenic effect, the evidence may not be relevant to humans, (4) results of short-term *in vivo* and *in vitro* tests provide additional information concerning a judgment of carcinogenicity of a chemical (OSTP, 1985, Principle #5, p. 10376), and (5) whether the methods used for statistical analysis are clearly stated and are generally accepted techniques for analyzing carcinogen bioassays (IARC, 1987, Suppl. 7, p. 26; OSTP, 1985, p. 10417).

The confidence in evidence of carcinogenicity derived from animal studies increases: With an increase in the number of responding species, strains, sites, dose levels, experiments, or unusual tumor types; with the

increase in the statistical significance of increased tumor incidence over controls; with dose-related increases in the proportion of malignant tumors and total tumors; and with shorter times between the start of chemical exposure and the onset of the tumor.

Benign tumors in experimental animals frequently represent a stage in the evolution of malignant neoplasms, but they may be endpoints that do not readily undergo transition to malignancy (IARC, 1987, Suppl. 7, p. 23; OSTP, 1985, p. 10416). However, if an agent is found to induce only benign neoplasms, it should be suspected of being a carcinogen and it requires further investigation. Consistent with this observation is a recent review of over 300 National Toxicology Program (NTP) cancer bioassays which found only a few chemicals (3%) causing only benign tumors (Huff, 1988). Thus, when benign tumors occur together with malignant tumors from the same cell type in an organ or tissue, the benign tumors should be combined with the malignant tumors for evaluating the carcinogenic effect (OSTP, 1985, principle 8, p. 10376; see McConnell et al., 1986 for guidelines for combining benign and malignant tumors).

In evaluating carcinogenicity studies, tumor data at sites with high background rates, such as testicular, pituitary, and mammary tumors in certain strains of rats and lung and liver tumors in certain strains of mice, may require special consideration (OSTP, 1985, p. 10417; principle #9, p. 10377). For example, in the case of the male B6C3F$_1$ mouse (which has a high background of liver tumors), if the only tumor response is the increase in liver tumors in males, the evidence will normally be considered "sufficient" evidence of carcinogenicity if the other criteria of "sufficient" evidence as outlined in the following section (such as, tumor response in another strain, species, or experiment) are met. However, the determination could be changed on a case-by-case basis to "limited evidence" if the liver response or other high background response is necessary for the original "sufficient evidence" determination but consideration of certain factors, stated below, relating to the high background response support such a change. Factors to be considered are: (1) The tumor incidence is increased only in the highest dose, and/or only at the end of the study; (2) the proportions of malignant tumors are not substantially increased in a dose-related manner; (3) the tumors are predominantly benign; (4) shortening of the time to the appearance of tumors did not occur in a dose-related manner; (5) negative or inconclusive results are obtained from a spectrum of short-term tests for mutagenic activity; and (6) excess tumors are found to occur only in a single sex (EPA, 1986).

c. *Comparison with EPA criteria.* The guidelines concerning carcinogenicity derived from evidence from animal studies agrees with criteria promulgated by EPA, except for the following differences.

i. The "No Data Available" and the "No Evidence of Carcinogenicity" classifications of EPA are not used because they are not necessary for the purpose of assessing the toxicity of consumer products. CPSC does not maintain an inventory of chemicals, as EPA does for all chemicals in commerce (except for drugs, food additives, and cosmetics), and therefore such categories are not needed.

ii. An increased incidence of benign tumors, with an indication that the tumors have the ability to progress to malignancy, is included as a contributing response in the criteria for "sufficient evidence" of carcinogenicity. Such evidence of carcinogenicity would not be treated this way by EPA's criteria. The Commission, after careful review of the available studies, has concluded that if a benign tumor is known to have the potential to progress to malignancy, then for all practical purposes the tumor should be considered to have the same potential health risk as if it is a malignant tumor. In addition, benign tumors in experimental animals frequently represent a stage in the evolution of a malignant tumor, as stated earlier.

iii. Increased tumor incidences at independent multiple sites of origin in the same species and study are considered as separate responses. Such evidence would be considered as a single response by the EPA's criteria. The Commission believes that the ability of a chemical to independently produce tumors at multiple sites indicates that it has a wide range of carcinogenic potential, similar to such an indication from responses in multiple strains, species, or experiments.

d. *Comparison with IARC's criteria.* The consideration of carcinogenicity derived from animal studies is also in agreement with that formulated by IARC, with the following exceptions.

i. The "Evidence Suggesting Lack of Carcinogenicity" classification is deleted since it is not necessary for the purpose of determining toxicity.

ii. According to IARC's criteria, increases in incidence rates of certain neoplasms that are known to have high background rates could be viewed as a "limited evidence," as opposed to a "sufficient evidence," classification. EPA's criteria, on the other hand, provide that such evidence should contribute to the "sufficient evidence" determination, which could be changed to "limited evidence" on a case-by-case basis, depending upon the specific information as described above in the section dealing with tumor data at sites with high background rates (EPA, 1986). The Commission, after careful review of available data, concludes that EPA's criteria provide a more thorough analysis of whether the high background rate of tumors is confounding the observed correlation between exposure and cancer.

iii. An increased incidence of benign tumors only, with an indication of the ability of the tumors to progress to malignancy, would contribute to the "limited evidence" classification by IARC's criteria. However, such evidence is viewed by the Commission as a contributing response in the criteria for "sufficient evidence" of carcinogenicity, for the reasons described above in section B.3.c.(ii) discussing how the criteria differ from EPA's classification scheme.

iv. Increased incidence of tumors at independent multiple sites of origin in the same species and study are treated as discussed above in section B.3.c.(iii) concerning differences from EPA's classification scheme. IARC's approach is similar to that of EPA's.

e. *ANSI definitions.* ANSI Z129.1 (1988) did not specify criteria for the evidence of carcinogenicity derived from animal studies, but it made use of animal data in its overall definitions of carcinogenicity.

f. *Categories of animal evidence.* Based on current information, the Commission concludes that the following classifications represent the best scientific assessment and are most appropriate to classify the evidence derived from animal cancer bioassay studies.

i. Sufficient evidence of carcinogenicity in animals. "Sufficient evidence" of carcinogenicity requires that the substance has been tested in well-designed and -conducted studies (*e.g.*, as conducted by National Toxicology Program, or consistent with the OSTP guidelines) and has been found to elicit a statistically significant ($p<0.05$) exposure-related increase in the incidence of malignant tumors, combined malignant and benign tumors, or benign tumors if there is an indication of the ability of such benign tumors to progress to malignancy: (a) in one or

both sexes of multiple species, strains, or sites of independent origin or in experiments using different routes of administration or dose levels; or (b) to an unusual degree in a single experiment (one species/strain/sex) with regard to unusual tumor type, unusual tumor site, or early age at onset of the tumor. The presence of positive effects in short-term tests, dose-response effects data, or structure-activity relationships are considered additional evidence. If evidence of carcinogenicity in animals is sufficient, the substance will be considered toxic, in the absence of adequate conflicting data.

ii. Limited evidence of carcinogenicity in animals. "Limited evidence" of carcinogenicity means that the substance has been tested and found to cause any of the following: (a) a statistically significant ($p<0.05$) exposure-related increase in malignant, benign, or combined malignant and benign tumors in one or both sexes of only one species, strain, and site and such evidence otherwise does not meet the criteria defined for "sufficient evidence" in the above section; (b) evidence derived from studies which can be interpreted to show positive carcinogenic effects but which have some qualitative or quantitative limitations with respect to particulars, such as doses, exposure, followup, survival time, number of animals/group, or reporting of the data, which would prevent consideration of the evidence as "sufficient" (category i above); or (c) an increase in the incidence of benign tumors if there is no indication of the ability of the tumors to progress to malignancy. If only "limited" animal data exist for a substance, the substance will not be considered toxic under the definition on the basis of the limited animal data.

iii. Inadequate evidence of carcinogenicity in animals. "Inadequate evidence" of carcinogenicity includes that evidence which cannot be placed into "sufficient" or "limited" categories, or which is derived from poorly conducted studies with major qualitative and quantitative limitations, such as inadequate doses, too few animals/group, poor survival, or inadequate reporting, so that there can be no interpretation of the data as showing either the presence or absence of a carcinogenic effect. Data in this category do not establish a substance as toxic.

C. Neurotoxicity

1. Introduction.

This section discusses "neurotoxicity" for purposes of providing guidelines concerning neurotoxicity. The discussion presents a synopsis of criteria for the determination of the neurotoxicity of substances based on animal or human data. All neurotoxic effects, except those immediate effects which are rapidly and completely reversible following a short-term exposure, are considered chronic effects in the guidelines.

This discussion reflects the Commission's assessment of the most current scientific knowledge and consensus in this field (WHO, 1986; EPA, 1985; Spencer and Schaumburg, 1985; Hartman, 1988; OTA, 1990). For substances where the available evidence does not meet this standard, or where there is controversy about how the evidence should be evaluated, the Commission may proceed by rulemaking, as provided in section 3(a) of the FHSA, or by enforcement actions on a case-by-case basis to resolve the question of whether the substance presents sufficient evidence of an ability to be neurotoxic in humans that the substance should be considered toxic.

Test methods to determine certain neurotoxicity endpoints (manifestation of a neurotoxicological effect) are available (Anger, 1985, 1986, 1989; Baker, *et al.*, 1990; Johnson and Anger, 1983; Hartman, 1988; Tilson, 1989; EPA, 1985; WHO, 1986). Several federal agencies regulating toxic substances and drugs have guidelines to evaluate neurotoxicity as a part of acute and chronic toxicity testing and safety evaluation. The EPA has published neurotoxicity test guidelines (EPA, 1985) and is currently developing neurotoxicity risk assessment guidelines.

The U.S. National Institute of Occupational Safety and Health (NIOSH) has recommended national strategies for the prevention of neurotoxic disorders (NIOSH, 1988). NIOSH has listed 65 historically established human neurotoxic agents, major sources of exposure to them, neurotoxic effects associated with various agents, and chemicals for which neurobehavioral effects have been reported.

Evidence of neurotoxicity is evaluated by the quality and adequacy of the data and consistency of responses induced by a suspect neurotoxicant. Criteria to evaluate evidence derived from human and animal neurotoxicity data and the associated terminology outlined in the following sections are based on those of the World Health Organization (WHO), NTP, EPA, and NIOSH.

Evidence for neurotoxicity comes largely from human studies and animal studies. The guidelines would evaluate the toxicity of a substance on the basis of potential neurotoxicity based on available human and animal data. Under the guidelines, substances would be considered to be toxic if "sufficient evidence" or "limited evidence" exists to demonstrate neurotoxicity from studies in humans. In addition, those substances for which there is "sufficient evidence" of neurotoxicity in animals are considered toxic except that evidence derived from animal studies that has been shown not to be relevant to humans is not included.

The criteria in these guidelines are not intended to be mechanically applied, but rather should be interpreted with the exercise of expert technical judgment.

a. *Definition of neurotoxicity.* Neurotoxicity is any adverse effect on the structure or function of the nervous system by any substance, physical, chemical or biological in nature. The term "adverse effect" as used here means any undesirable effect on the nervous system caused by direct or indirect actions on the nervous system following acute, subchronic, or chronic exposures. The effect may be immediate or delayed, reversible or irreversible.

Characteristics of "adverse effects" include the following: (1) Side effects (unwanted effects) or effects due to overdosing; (2) functional or structural responses in the nervous system that promote compensation to restore normal function; or (3) any alteration from baseline (the individual's particular normal state), although still within "normal" range, which may diminish the ability to survive, undergo repair, or adapt to the environment. This definition includes chemicals that act directly on elements within the nervous system, such as glutamate which directly stimulates receptors, or indirectly, such as carbon monoxide which decreases the availability of oxygen.

"Adverse effects" must be considered within the context of agent usage and exposure scenario (ICON, 1990).

b. *The nervous system: Background and definition.* Effects on the nervous system will be considered in relation to the two major anatomical divisions: central and peripheral. The central nervous system consists of the parts of the nervous system contained within the skull (brain) and the vertebral column (spinal cord). The peripheral nervous system consists of nerve cells (neurons)

and their processes (axons, dendrites) which conduct information between muscles, glands, sense organs, and the spinal cord and brain. The peripheral nervous system includes afferent (sensory) and efferent (motor) fibers; both types of fibers are represented in the components of the nervous system (WHO, 1986).

Basic cellular elements of the nervous system are neurons, glial cells associated with blood vessels, and other specialized epethelial and connective tissue cells (WHO, 1986). Neurons contain multiple short processes, called dendrites, which receive information from other nerve cells, and a single long axon that conducts electrical signals to other neurons and muscles, and to and from skin, muscles, and glands. The axon terminates at a synapse where chemically-encoded information is conveyed to neurons or muscles. Glial cells in the central nervous system comprise the supporting structure of nervous tissue.

Neurons are atypical cells because the dendrites and the axon are metabolically inactive and collectively are much larger than the cell body (somata), which alone is responsible for all the metabolic activity required for maintenance of the entire cell (WHO, 1986). The structure of neurons provides an enormous surface area for chemical exposure, and consequently, chemical injury. For example, a peripheral neuron located in the lumbar portion of the spinal cord and innervating a muscle in the foot is about a meter long and contains a long column of cytoplasm.

Some chemicals may interfere in the maintenance of this cytoplasm column by, for example, interrupting transportation of nerve impulses along the axon. In this way a chemical such as n-hexane, and n-methylbutyl ketone may affect the nervous system. Chemicals such as triethyl tin may induce changes in the metabolic system of the somata, which may then cause degenerative changes in the entire neuron. A chemical such as triethyl tin, hexachlorophene, or lead, may alter myelinating cells (myelin is a fatlike substance forming a sheath around certain nerve fibers), cytoplasmic processes, or the myelin sheath, thereby causing neurotoxic effects. Intracellular elements of intraneural blood vessels may be altered by chemicals such as lead and misonidazole. Secondary changes may then occur in other tissues, such as voluntary muscles (WHO, 1986).

Several means exist for chemicals to enter the nervous system. Although the nervous system is largely protected from chemicals entering into nerve cells through blood, the blood-brain barrier is not complete. Some chemicals, especially the lipid soluble type, may still cross the barrier. Another mode of entry of chemicals is by uptake into peripheral nerve terminals. The chemical is then transported to the cell bodies in the CNS through the axon. Parts of the nervous system such as neurons of the autonomic nervous system and the sensory ganglia, certain parts of the brain (*e.g.*, near the beginning of the spinal cord), and to a limited extent, the retina in the eye, are outside the blood-brain barrier and are likely to be more exposed to neurotoxic chemicals than are other parts (WHO, 1986).

Some other factors that may influence susceptibility to effects are the size and type of the nervous system cell, the level and type of the various neurotransmitters in different regions of the nervous system, the integrity of cellular membranes, the type of intracellular organelles, and the degree of vascularity (Baker, *et al.*, 1990). For example, a poorly vascularized (*i.e.*, has fewer vessels) nervous tissue, such as the globus pallidus, is likely to be more susceptible to hypoxia (abnormal condition resulting from decrease in oxygen supplied to or used by body tissue) than a more vascularized tissue of the nervous system, such as the cerebral cortex. However, in some cases where cells have a high requirement for oxygen, they may be more sensitive to hypoxia in spite of the high vascularization than less vascularized tissue having a low requirement for oxygen. For example, neurons of the grey matter of the cerebral cortex are more vascularized than the myelinated axons of the cerebral white matter. However, the neurons are more sensitive than the axons to hypoxia because they have a higher requirement for oxygen than the axons for metabolism.

c. *Manifestations of neurotoxicity.* Common manifestations of neurotoxicity may be categorized into four types: sensory effects, motor effects, autonomic effects, and pathophysiological effects (changes to the structure and function of nerve cells and tissue).

Common signs and symptoms of sensory effects include anxiety, irritability, apathy, lethargy, attention difficulty, illusion, delusion, hallucinations, dementia (mental deterioration), depression, euphoria, stupor (partial or nearly complete unconsciousness), and coma. Other signs and symptoms of sensory effects are abnormalities of (a) smell, vision, taste, hearing, skin senses (for example, numbness, pain); (b) proprioception (reception of information given by sensory nerve terminals concerning movements and position of the body; it occurs chiefly in the muscles, tendons, and the labyrinth).

Common signs and symptoms of cognitive effects include effects upon short-term memory, learning, verbal and non-verbal long-term memory, problem solving, attentional and arousal decrement and vigilance disturbances.

Common signs and symptoms of motor effects are muscle weakness, abnormal body posture or gait, paralysis, spasticity, rigidity, tremor, dystonia (abnormal muscle tone), incoordination, hyperactivity, myoclonus (alternate cycles of rigidity and spasm in rapid succession of a muscle or of a group of muscles), fasciculations (spontaneous contractions of a number of muscle fibers supplied by a single motor nerve filament), cramps, seizures, and convulsions.

Common signs and symptoms of autonomic effects are abnormalities in control of functions related to (a) temperature that may be manifested, for example, in sweating; (b) the gastrointestinal tract that may be shown in diarrhea, salivation, or a change in appetite; (c) the cardiovascular system, for example, a change in heart rate; and (d) changes in other functions, such as, urination, sexual functions, and lacrimation (tearing).

Common pathophysiological effects on the nervous system are as follows: (a) Neuronopathies (partial or complete loss of the neuronal cell body, its processes, collaterals, or terminations); (b) myelinopathies (segmental or focal demyelination which means destruction of myelin, a fatlike substance forming a sheath around certain nerve fibers); (c) axonopathies (axonal degeneration); (d) disruptions in synaptic transmission (synthesis, storage, degradation, transport, release, and binding to specific membrane receptors of neurotransmitter chemicals); (e) changes in levels and functions of ion channels (sodium and potassium ions responsible for depolarizing and repolarizing the membrane respectively) and changes in related enzymes such as neurotoxic esterases.

2. Evidence of Neurotoxicity: General Discussion

Evidence of neurotoxicity is derived from toxicological studies related to neurobehavior, neurochemistry, neuropathophysiology, and neurodevelopment in humans and in animals. Major objectives of a neurotoxicity study are to detect and

characterize toxicity endpoints, identify changes in the structure and function of the nervous system, characterize the changes associated with exposure, assess the existence of any dose-time-response association, and elucidate the mechanism of neurotoxicity (Hartman, 1988; WHO, 1986).

Neurobehavioral studies determine the effect of a chemical exposure based on observations of the behavioral functions of the subject. Some of the behavioral functions generally tested in these studies are motor speed and steadiness, attention/response speed, manual dexterity, visual perception/memory, auditory memory, verbal abilities, attention/vigilance, profiles of mood state, and respondent and operant behavior.

Neurochemical studies determine the effect of chemical exposure on changes in the level, activity, and pattern of neurotransmitter chemicals, such as acetylcholine, noradrenaline, dopamine, glycine, serotonin, and of enzymes like neurotoxic esterases.

Neuropathophysiolgical studies determine the effect of chemical exposure on the structure and function of the nerve tissues. Observed effects and types of studies include: (1) Degeneration, or demyelination of nerve tissues; (2) encephalography (electrical activity measurements of the brain); (3) evoked potential (electrical phenomena evoked in the brain by external activity such as auditory, visual, or somatosensory stimuli); (4) electromyography (recording electrical activity from a muscle); (5) electroneurography (measurement of both motor and sensory nerve conduction velocities); (6) temperature threshold; and (7) quantitative testing for cutaneous (skin) sensation.

Developmental neurotoxicity studies are concerned with adverse effects on the structure of the nervous system or on neurobehavioral functions related to physical growth and development (Wier, *et al.*, 1989).

Several major difficulties in determining neurotoxicity of chemicals exist. Problems may arise regarding the ability of the nervous system to conform with the immediate environment, due to the scientific community's incomplete understanding of the neurotoxic effects, due to interspecies differences in structure and complexity of functions, and due to a very wide range of normal neurological and physiological functions of the nervous system which can mask the ability to observe effects due to chemical exposure. Suitable methods are unavailable to detect changes with a reasonable degree of certainty in adaptive capacity of the nervous system, in homeostatic functioning, as well as in movement pattern, fatigue, and the ability to perform complex tasks. It is, therefore, clear that a single test may not suffice to detect neurotoxicity (WHO, 1986).

Evidence for neurotoxicity comes from two sources, namely, studies in humans and studies in animals. Results from these studies are evaluated in view of the available information on histopathology (changes in tissues), enzyme inhibition, metabolism, and other relevant toxicological data to determine if there is a causal association between exposure to a chemical and neurotoxicity.

3. Evidence of Neurotoxicity Derived From Studies in Humans

a. *Discussion.* Direct evidence of human neurotoxicity comes from observations of humans. A good quality human study should have a clear and detailed description of the studied population, disease, and exposure. A neurotoxicant can produce more than one neurotoxic effect including those related to sensory, motor, learning/memory, or mood activity. The history of occurrence of the effect should be relatively complete, and past events should be substantiated by medical records if possible. The design of the study should have dealt with bias and confounding factors that can influence the risk of disease by matching, or in the analysis by statistical adjustments. The study should describe the determination of statistical parameters, such as relative risk, odds ratio, absolute disease rate, confidence intervals, significance tests, and adjustments made for confounding factors. It should also describe the selection and characterization of exposed and control populations, size of the population groups, adequacy of duration, completeness, and quality of follow up. A causal association is strengthened by the observation of a dose-response relationship, consistency and reproducibility of results, strength and specificity of the association, and an established mechanism of action.

The evaluation of human neurotoxicity studies should consider many factors including: Age, sex, socioeconomic status, health, neurological disorders and other diseases, drug treatment history, recreational drug use, motivation of the test and reference groups, life style (alcohol, smoking, etc.), education level, individual levels of alertness, emotional state, and levels of sleep and fatigue. Tests should be blind and test sites free from distractions. Confounding factors to be considered in evaluation of these studies include allergic and idiosyncratic reactions. Other complex issues to be considered are: immediate versus delayed toxicity, reversible versus irreversible effects, local versus systemic effects, acute versus chronic effects, and tolerance development (Hartman, 1988; OTA, 1990; Anger, 1989; Jonson and Anger, 1983; Hooper, 1987).

Major difficulties encountered in studies in humans are the delayed neurotoxic effects, exposures to mixtures of chemicals, and the lack of information on the effects of acutely non-toxic low-dose levels of neurotoxicants over a long period of time.

b. *Evidence of neurotoxicity derived from studies in humans.* Since neurotoxic effects are very complex and often subtle in nature, scientific judgment is necessary in classifying the evidence. The confidence in evidence of neurotoxicity derived from human studies increases with the observation of a dose-response relationship, consistency and reproducibility of results, strength and specificity of the association, and conformance with an established mechanism of action.

i. Sufficient evidence of neurotoxicity. "Sufficient evidence" for a causal association between exposure to a chemical and neurotoxicity is considered to be present when the following four criteria are met. (1) A consistent pattern of neurological dysfunction is observed in multiple studies. (2) The adverse effects/lesions in the nervous system account for the neurobehavioral dysfunction with a reasonable degree of certainty. (3) All identifiable bias and confounding factors are discounted after consideration. (4) Based on statistical analysis, the association has been shown unlikely to be due to chance with reasonable certainty.

ii. Limited evidence of neurotoxicity. "Limited evidence" of neurotoxicity means that evidence is less than convincing, *i.e.*, one of the above "sufficient evidence" criteria for establishing a causal association is not met. Thus, uncertainties exist in establishing the association between exposure to a chemical and the neurotoxic effect.

iii. Inadequate evidence of neurotoxicity. "Inadequate evidence" of neurotoxicity means that evidence does not meet the criteria of the above two categories and that no interpretation of the data shows either the presence or absence of a chemical exposure-related neurotoxic effect.

4. Evidence of Neurotoxicity Derived From Studies in Animals

a. *General considerations.* In the absence of human data, the next best source of evidence of neurotoxicity is animal data which may be considered relevant to humans for the following reasons: (1) Anatomy, physiology, histology, and biochemistry of the nervous system in humans and mammals are essentially similar; (2) chemical agents first found to be neurotoxic in humans, such as methylmercury, carbon disulfide, n-hexane, methyl ethyl ketone, methyl butyl ketone, and dichloroacetaldehyde are also neurotoxic in animals; and (3) agents, like aluminum and pyridoxin phosphate (vitamin B6), first identified in animal studies as neurotoxic were later found to be neurotoxic in humans (WHO, 1986). In neurotoxicity studies, animals are dosed acutely, subchronically, or chronically. Neurotoxicity endpoints are studied using different test methodologies designed either to screen or investigate a mechanism of action of neurotoxicity, or to gather additional data.

Criteria for assessing quality and adequacy of animal studies have been discussed by various groups (WHO, 1986; EPA, 1985; Hartman, 1988; Tilson, 1987, 1989; OTA, 1990). The major factors indicative of a good quality animal study are the following. (1) Species, sex, age, health, housing conditions, and nutrition of the animals are suitable for the test. (2) The number of animals/group/sex are adequate. (3) Animals are randomly distributed in the groups. (4) Dose levels, duration, and frequency selected are adequate to detect the adverse neurotoxic effects. (5) Data collection and reporting are complete and clear. (6) Routes and exposure pattern are relevant to the human situation. (7) Test methods used for statistical analysis are appropriate, clearly stated, and are the generally accepted techniques for analyzing neurotoxicity studies (WHO, 1986; EPA, 1985; Hartman, 1988; Tilson, 1989; OTA, 1990).

A good quality animal study requires consideration of reliability, sensitivity, and validity of the results (Vorhees, 1987). Interpretation of neurotoxicity data should consider: (1) If the neurotoxic effects are caused by a single dose (such as cholinesterase inhibitors and pyrethrins); (2) if effects are reversible or irreversible (reversible effects may indicate compensation or adaptation rather than a simple acute effect); (3) if neurotoxicity is delayed; (4) if a threshold exists (effects may appear only after changes in the nervous system caused by repeated exposures have reached a threshold limit); and (5) if circadian rhythms may influence behavior, such as, feeding, drinking, sleeping, and mating (WHO, 1986).

b. *Categories of neurotoxicity studies.* Six common representative categories of neurotoxicity studies, with a few examples of test methods in each category, to determine various neurotoxicity endpoints are listed below.

i. Neurobehavioral studies are concerned with adverse effects of a chemical on the behavior of an organism. Behavior may be defined as movement of an organism or its parts within contexts pertaining to time and space. Behavioral responses typically have been divided into three types based on the functional relations that control their occurrence (WHO, 1986). These three types are respondent behavior, operant behavior, and mixed behavior.

Respondent behavior is controlled mainly or exclusively by the prior occurrence of an event (stimulus) in the environment. The events are referred to as eliciting stimuli. A classic example of unconditioned respondent behavior is a dog's salivation when food, an unconditioned stimulus, is placed in the dog's mouth.

Operant behavior is apparent exclusively from its consequences and is also referred to as emitted behavior. Operant behavior occurs with no known observable eliciting stimulus. For example, when an animal is exposed to a novel environment, it will show a characteristic pattern of exploratory activity initially, followed by a slowdown. The environment is not an eliciting stimulus. However, the motor activity is associated with the environment.

Some behavior, known as mixed behavior, is known to have both respondent and operant components. For example, bird pecks are controlled partly by eliciting stimuli and partly by response consequences.

Both respondent and operant behaviors may be modified by the conditioning (learning) process. For example, when food (a non-conditioning stimulus) is placed in a dog's mouth only after a special note is sounded (a conditioning stimulus) and the procedure is repeated for some time, the sound of the note alone starts inducing salivation, without placing food in the dog's mouth: a conditioned respondent behavior. A conditioned operant behavior occurs, for example, when a food-deprived rat is placed in a chamber with a food dispenser and a lever, and the depression of the lever results in presentation of food, then the consequence of the behavior (pressing the lever and presentation of food) comes to control the occurrence of the response.

Common neurobehavioral studies include detection and evaluation of changes in the following neurotoxicity endpoints: cognitive functions; eating and drinking behavior; social behavior involving two or more individuals; tremors, convulsions (threshold dose of convulsants is considered in view of other unrelated toxicity), ataxia (effects on muscular coordination), paralysis, lacrimation, and the presence and absence of certain reflexes; spontaneous motor activity; motor functions; and sensory processes.

ii. Neurophysiological studies basically measure various physiological functions; such as, (1) nerve conduction velocity, (2) peripheral nerve terminal function, (3) electromyographic activity, (4) spinal reflex excitability, (5) electrocardiographic activity (EKG), (6) blood pressure, (7) electroencephalographic activity (EEG), (8) general excitability, (9) convulsive activity, (10) stimulation of the cerebral motor cortex, (11) recovery functions, (12) cognitive functions, and (13) synaptic and membrane activity.

iii. Morphological studies assess structural changes in neural and non-neural cells of the nervous system. Such changes may include: (1) The accumulation, proliferation, or rearrangement of structural elements like intermediate filaments, microtubules, or organelles (*e.g.*, mitochondria, lysosomes); (2) the degeneration of neural cells in whole or in part; (3) gross changes in morphology of cells; (4) changes in brain weight; (5) discoloration of and hemorrhage in nerve tissue; and (6) changes in glial and fibrillary acidic protein (GFAP).

iv. Biochemical and endocrinological studies may include determination of changes in: (1) RNA, DNA, and protein synthesis in nerve cells; (2) enzyme levels; (3) lipids, glycolipids, and glycoproteins synthesis; (4) synthesis, uptake, release, reuptake, metabolism, stimulation and inhibition of acetyl choline, epinephrine, serotonin and other neurotransmitters; (5) ion channels and energy metabolism; (6) anterior pituitary hormones, *e.g.*, follicle stimulating hormone, thyrotropic hormone, hypothalamic control of pituitary secretions; and (7) peripheral metabolism of endocrine secretions.

v. Developmental neurotoxicity studies consist of a battery of tests to evaluate physical growth/

developmental and neurobehavioral functions. The tests given at the preweaning stage, for example, may include measuring brain weight and pup weight, and monitoring physical development at various intervals of time. Examples of the tests given at the postweaning stage are tests of sensory and neuromuscular functions, reactivity, problem solving, and neuroendocrine functions. (Wier, *et al* 1989). Neurotoxic agents may cause qualitatively different toxicity syndromes in developing animals than in adult animals.

vi. *In vitro* neurotoxicity studies may be used to support the animal studies. However, they are not considered adequate by themselves to classify neurotoxicants. These studies generally use primary cell cultures of various tissues, such as adult mouse sensory neurons, rodent fetal cells, and cerebellar cells. The studies may also use free-living soil nematodes, *e. g., caenorhabditis elegans,* and various microorganisms (Harvey, 1988; Reinhartz, *et al.,* 1987; Davenport *et al.,* 1989; Williams, *et al.,* 1987).

vii. Other studies may include studies dealing with pharmacokinetics, blood-brain barrier, bioavailability, and structure-activity relationships.

c. *Classification of neurotoxicity evidence derived from studies in animals.* Because of the complex and often subtle nature of the neurotoxic effects, scientific judgment is necessary in classifying neurotoxicity evidence. The confidence in evidence of neurotoxicity derived from animal studies increases (becomes convincing) with (1) an increase in the number of responding species, strains, dose-levels, experiments, severity and multiplicity of effects; (2) the observation of a dose-response relationship, consistency and reproducibility of results, and specificity and strength of the association; (3) supportive *in vitro* and other studies; and (4) an increase in statistical significance of neurotoxic effects over controls.

1. Sufficient evidence of neurotoxicity. "Sufficient evidence" for a causal association between exposure to a chemical and neurotoxicity means that (1) the substance has been tested in well-designed and -conducted studies (*e.g.,* NTP's neurobehavioral test battery, Tilson 1989; EPA's neurotoxicity test guidelines, EPA, 1985), and (2) the substance has been found to elicit a statistically significant ($p < 0.05$) increase in any neurotoxic effect in one or both sexes of multiple species, strains, or experiments using different routes of administration and dose-levels.

Evidence derived from animal studies that has been shown not to be relevant to humans is not included. Such evidence would result, for example, when there was an identified mechanism of action for a chemical that causes neurotoxicity in animals that has been shown not to apply to the human situation. For example, metabolic-pharmacokinetic properties concerning the need for activation of the agent to produce neurotoxicity may come into play. If humans do not have the same metabolic pathway found necessary in the test animal for the neurotoxic effect, then the study may not be relevant to humans.

ii. Limited evidence of neurotoxicity. "Limited evidence" of neurotoxicity means that the substance has been tested and (1) found to cause a statistically significant ($p < 0.05$) increase in a neurotoxic effect in one or both sexes of only one species, strain, and experiment and such evidence otherwise does not meet the criteria defined for "sufficient evidence" above; or (2) evidence derived from studies which can be interpreted to show positive neurotoxic effects, but have some qualitative or quantitative limitations with respect to particulars, *e.g.,* doses, exposure, follow-up, number of animals/group, and reporting of the data, which would prevent classification of the evidence as "sufficient" in the category above.

iii. Inadequate evidence of neurotoxicity. "Inadequate evidence" of neurotoxicity means that evidence does not meet the criteria of the above categories and that there can be no interpretation of the data as showing either the presence or absence of a chemical exposure-related neurotoxic effect. Data in this category would not establish a substance as toxic under the guidelines.

D. Reproductive and Developmental Toxicity

1. Introduction

a. *General discussion.* This section discusses the guidelines concerning reproductive and developmental toxicity. Section 2(g) of the FHSA defines toxic as applying "to any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface." 15 U.S.C. 1261(g).

The Commission is issuing these guidelines to specify criteria that will offer consistent guidance for identifying developmental or reproductive toxicants. This guidance reflects the Commission's assessment of the most current scientific knowledge and consensus in this field.

The intent of the guidelines is to incorporate those areas in which there is a substantial consensus as to the evidence needed to support a conclusion that a substance is a likely human developmental or reproductive toxicant. For substances where there is controversy about how the evidence should be evaluated, the Commission may proceed by rulemaking, as provided in section 3(a) of the FHSA, or by enforcement actions on a case-by-case basis to resolve the question of whether the substance presents sufficient evidence of an ability to produce developmental or reproductive toxicity in humans so that the substance should be considered toxic.

Evidence for developmental or reproductive toxicity largely comes from two sources: Human studies (epidemiology) and animal studies. Results from these studies are supplemented with available information from short-term tests, pharmacokinetics, and other relevant toxicological data. The guidelines issued by the Commission evaluate the toxicity of a substance on the basis of developmental or reproductive toxicity based on human and animal data. Under the guidelines, substances would be considered to be toxic if "sufficient evidence" or "limited evidence" exists to demonstrate developmental or reproductive toxicity from studies in humans. In addition, those substances for which there is "sufficient evidence" of developmental or reproductive toxicity in animals are considered toxic, except that evidence derived from animal studies that has been shown not to be relevant to humans is not included.

As noted above, it will be necessary to continue to rely on rulemaking under section 3(a) of the FHSA, or on enforcement actions, to resolve uncertainties that are not addressed by these guidelines. In this regard, the Commission notes that the criteria stated in the guidelines do not lend themselves to unambiguous application. A number of the criteria include statements that themselves can be interpreted only by the exercise of expert technical judgment. For example, one of the factors stated below for determining that an epidemiological study shows a causal relationship between exposure to an agent and developmental or reproductive toxicity is that confounding factors such as socioeconomic status, age, smoking, alcohol consumption, drug use, environmental or occupational exposure, and other diseases should be

adjusted for. Expert technical judgment is required to identify possible confounding factors and to evaluate whether the available data are adequate to eliminate such factors as causes of the observed association. In some instances, this will not be straightforward. The guidelines will not resolve such controversy, and it may be appropriate for the Commission to conduct rulemaking to resolve the controversy or bring enforcement actions in which the toxicity of the substance would be established on a case-by-case basis.

Although there are many difficult issues related to the interpretation of developmental or reproductive toxicity studies in animals and humans, criteria for defining developmental or reproductive toxicity have been established by several groups, such as the Food and Drug Administration (FDA), the EPA, and the European Economic Community (EEC). The Commission also believes that this approach for defining known or potential developmental or reproductive toxicants in consumer products is appropriate and feasible. The evidence of developmental or reproductive toxicity is determined by the quality and adequacy of the data and the consistency of responses induced by a suspect developmental or reproductive toxicant.

The following paragraphs describe definitions and terminology used in this section and suggest guidelines for identification and classification of reproductive and developmental toxicants. These guidelines may be used as a basis for labeling of consumer products under the FHSA.

b. *Definitions and terminology.* For these guidelines, the following definitions and terminology will be used. Some of these definitions were adapted from EPA (1988a), EPA (1988b), EPA (1989), and the Medical Dictionary by Saunders (1965).

Altered growth: An alteration in offspring organ or body weight or size.

Blastocyst: A structure resulting from the repeated divisions of the fertilized ovum.

Conceptus: The whole product of conception at any stage of development from fertilization of ovum to birth.

Developmental toxicity: Adverse effects on the developing organism that may result from its exposure during prenatal development, or postnatally to the time of sexual maturation. The adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (1) Death of the developing organism, (2) structural abnormalities, (3) altered growth (4) functional deficiencies, and (5) behavioral deficiencies.

Embryo: Developing young in the human uterus before eight weeks. The time period varies from one species to another in animals.

Embryotoxicity: Any toxic effect on the embryo as a result of prenatal exposure. These include malformations, altered growth and in utero death.

Epididymis: The elongated cordlike structure along the posterior border of the testis, containing ducts in which sperm are stored.

Estrogen: A female sex hormone secreted by the ovary.

Estrous cycle: The cycle of changes in the female genital tract of lower mammals, which are produced as a result of ovarian hormonal activity. It is equivalent to the menstrual cycle in humans and other primates.

Female reproductive toxicant: An agent which can adversely affect the ability of a sexually mature female to produce normal offspring.

Fertility: The capacity to conceive or induce conception.

Fertilization: The fusion of a sperm with an ovum resulting in the formation of a zygote.

Fetotoxicity: Any toxic effect on the fetus as a result of prenatal exposure. These include malformations, altered growth and in utero death.

Fetus: Developing young in the human uterus after eight weeks. The time period varies from species to species in animals.

Follicle Stimulating Hormone (FSH): A pituitary hormone responsible for the development of ova and production of estrogen in females, and the development of seminiferous tubules and production of sperms in males.

Gonad: An ovary or testis.

Implantation: Attachment of the blastocyst to the epithelial lining of the uterus.

Luteinizing Hormone (LH): A pituitary hormone responsible for ovulation, development of corpus luteum, and production of progesterone in the females, and production of testosterone in males.

Male reproductive toxicant: An agent which can adversely affect the ability of a sexually mature male to produce normal offspring.

Malformation: A permanent structural change that may adversely affect survival, development, or function.

Neonate: Newborn.

Ova: Plural of ovum.

Ovary: The female gonad.

Ovum: The female reproductive cell.

Pituitary gland: A gland which is located in the brain and secretes many hormones which control growth and functions of many organs of the body including the testis in males and the ovary in females.

Postnatal: After birth.

Prenatal: Before birth.

Progesterone: An ovarian hormone primarily responsible for the maintenance of pregnancy.

Prostate: An accessory male sex gland which secretes a part of semen.

Seminal plug: A wax like material found in the vagina of the female rodents approximately 12–24 hours after successful mating.

Seminal vesicle: An accessory male sex gland which secretes a part of semen.

Sperm: The male reproductive cell.

Teratogen: An agent or factor that causes the production of a structural defect in the developing embryo or fetus.

Testis: The male gonad.

Testosterone: The male sex hormone secreted by testis.

Variation: A structural deviation that may not adversely affect survival, development, or function.

2. Identification of Developmental and Reproductive Toxicity Hazards from Studies in Humans

a. *Discussion.* Good epidemiologic studies provide the most relevant information for assessing human risk. Epidemiologic data are obtained from occupational, environmental, therapeutic, or consumer exposure to a substance. A positive good quality epidemiologic study should meet the following criteria (EPA, 1988a; EPA, 1988b; EPA, 1989): (1) There should be no identifiable bias which can be introduced through a faulty design of the experiment. For example, if hospital records are used, embryonic or early fetal loss may be underestimated since women are not necessarily hospitalized for these outcomes. These parameters may be better ascertained by random interviews. (2) Confounding factors such as socioeconomic status, age, smoking, alcohol consumption, drug use, environmental or occupational exposure, and other diseases should be adjusted for. (3) The association between an endpoint and a causal factor should not be due to chance; there must be a statistically significant association.

b. *Categories of human evidence.* The following categories of evidence from human studies have been developed.

i. Sufficient evidence of developmental or reproductive toxicity in humans. The evidence for a substance causing an adverse reproductive or developmental effect(s) is considered sufficient when it is based on good

quality human epidemiology which meets all the requirements stated in the above discussion of human studies; the results are statistically significant and without identifiable bias or confounding factors.

ii. Limited evidence of developmental or reproductive toxicity in humans. The evidence for a substance causing an adverse reproductive or developmental effect(s) is considered limited when the human epidemiology meets the criteria for sufficient evidence except that it lacks one of the criteria described in the above discussion of human studies. Thus, evidence is limited when statistical significance is borderline as opposed to clear-cut, there is a source of bias, or there are confounding factors that have not been or cannot be corrected for.

iii. Inadequate evidence of developmental or reproductive toxicity in humans. The evidence is considered inadequate when more than one of the above criteria for establishing a causal association between exposure to the agent and reproductive or developmental effects are not met, leaving an alternative explanation to be equally likely.

3. Identification of Developmental and Reproductive Toxicity Hazards from Studies in Animals

Although human data are most relevant for predicting human hazard, in its absence animal information becomes a valuable tool for predicting effects in humans. Many chemicals which are reproductive and developmental toxicants in humans have been shown to produce similar effects in animals (Council on Environmental Quality (CEQ), 1981). Some examples are alcohol, busulfan, chlorobiphenyls, diethylstilbestrol, isotretinoins, organic mercury, thalidomide, valproic acid, aminopterin, lead, ethylenedibromide, kepone, and carbondisulfide (CEQ, 1981; EPA, 1989). In a review by FDA (1980) of 38 compounds known to be associated with birth defects in humans, 37 were found to produce similar effects in at least one species of animals (45 FR 69,823). In another review of the data of the teratologic potential of 203 chemicals by FDA (1980), FDA stated: "it is reasonable to conclude that positive animal teratology studies are at least suggestive of potential human response." (45 FR 69,824). In addition, Wilson (1977) has described the mechanism(s) and pathways which could be applicable to both humans and animals in the initiation and development of birth defects.

a. *Study protocols for studying developmental and reproductive toxicity in animals.* EPA has developed protocols for studying developmental, male reproductive, and female reproductive toxicities in laboratory animals. Each of these three study protocols is discussed briefly below.

A protocol for studying developmental toxicity has been described by EPA (1989). Developmental toxicity can be studied in animals by administering a test substance during pregnancy, and evaluating embryonal, fetal, and/or neonatal toxicity. The protocol may also include exposure of the organism during a specific period of development (*e.g.*, during organ development), evaluation of toxicity over several generations, evaluation of toxicity during the early postnatal period or even up to sexual maturity. Animals used for developmental toxicity studies are usually mice, rats, or rabbits The most important endpoints of developmental toxicity are embryonal mortality, fetal mortality, neonatal mortality, malformations (external, visceral, skeletal) at any stage of development, altered growth, as well as functional and behavioral abnormalities.

A protocol for studying male reproductive toxicity has been described by EPA (1988a). Male reproductive toxicity can be studied by exposing sexually mature male rats to a test substance for a certain period followed by cohabitation with untreated sexually mature female rats. The exposure of the males to the test material is continued during the mating period. The main endpoints for evaluating toxicity are mating ability, fertility, prenatal and postnatal developmental effects, and weight and histopathological evaluations of reproductive organs (testis, epididymus, prostrate, seminal vesicle and pituitary). Mating ability is ascertained by determining the number of animals with seminal plugs or the presence of sperm in a vaginal lavage, per number of pairs of rats cohabited. Fertility is ascertained by determining the number of animals pregnant per number of confirmed matings. The prenatal and postnatal developmental effects are ascertained by determining litter size, pre- and post-implantation loss, number of live and dead pups, sex ratios, malformation, birth and postnatal weight, and survival. Positive findings for supplemental endpoints such as sperm evaluation (count, morphology, and motility) and hormone evaluation (testosterone, FSH, and LH) increase the evidence for hazard identification.

EPA has also described a protocol for studying female reproductive toxicity (1988b). Female reproductive toxicity can be studied by exposing sexually mature female rats to a test material for a certain period followed by cohabitation with untreated sexually mature male rats. Exposure of females to the test material is continued during the mating period and throughout gestation and lactation. The main endpoints for evaluating toxicity are mating ability, fertility, prenatal and postnatal developmental effects, weight and histopathological evaluations of reproductive organs (ovary, uterus, and pituitary). Positive findings for supplemental endpoints such as estrous cycle abnormalities, and hormone evaluations (estrogen, progesterone, FSH, LH) increase the evidence for hazard identification.

Studies on reproductive toxicity are often performed where both males and females are treated, in a manner such as described above for the individual sexes. Such studies may not distinguish between "male" and "female" reproductive toxicity.

b. *Criteria for a good quality developmental or reproductive toxicity animal study.* Any reliable study of developmental or reproductive toxicity should be designed and carried out in accordance with certain recognized criteria. The following criteria should be met for a good quality developmental or reproductive toxicity animal study.

1. The study should include at least one dosed (treated) group and one concurrent control group. However, two or more differently dosed groups are preferred.

2. Maternal toxicity (*e.g.*, a reduction in maternal body weight or organ weight) should be evaluated and accounted for in the interpretation of a study. In an ideal situation, the toxic effect(s) observed in a positive study are significant at one or more doses in the absence of maternal toxicity. However, such toxicity is not automatically discounted as secondary when associated with maternal toxicity.

3. Test animals are selected based on consideration of species, strain, age, weight and health status, and should be randomized into dose groups in order to reduce bias and provide a basis for performing valid statistical tests.

4. Good historical data on developmental and reproductive toxicity should be available for the species/strain tested; ideally, such data should be obtained for animals from each supplier.

5. The number of animals per dose group should be adequate. Generally, 20 litters per group for rodents and 12 litters per group for rabbits are used (Sowinski, *et al.*, 1987).

6. Toxicity is evaluated using acceptable laboratory methods, and

data are analyzed using appropriate statistical methods.

Sufficient evidence derived from animal studies is used as a basis to predict probable developmental or reproductive toxicity of an agent in humans. The evidence for toxicity derived from animal studies is supported by observance of (1) dose-related effects over an increased number of doses, (2) an increased number of different endpoints, (3) the same route of exposure as the expected human exposure route, (4) multiple species/strains, or routes of administration exhibiting the response(s), and (5) pharmacokinetic data and information on the likely mechanism of action.

c. *Categories of evidence for developmental or reproductive toxicity derived from animal studies.* The following categories of animal evidence have been developed.

i. Sufficient evidence of developmental or reproductive toxicity in animals. The evidence for a substance is considered sufficient when obtained from a good quality animal study and there is a statistically significant ($p < 0.05$) treatment-related increase in multiple endpoints (as described in the toxicity study protocol section) in a single species/strain, or in the incidence of a single endpoint at multiple dose levels or with multiple routes of administration in a single species/strain, or increase in the incidence of a single endpoint in multiple species/strains/experiments. Evidence from animal studies which has been shown to be not relevant to humans is not used for this purpose.

ii. Limited evidence of developmental or reproductive toxicity in animals. The evidence for a substance is considered limited when (1) obtained from a good quality study and there is a statistically significant ($p < 0.05$) treatment-related increase in the incidence of a single endpoint in a single species/strain/experiment at a single dose level administered through only one route and such evidence otherwise does not meet the criteria defined for "sufficient evidence" above; or (2) the evidence is derived from studies which can be interpreted to show positive effects but have some qualitative or quantitative limitations with respect to experimental procedures (*e.g.*, doses, exposure, follow-up, number of animals/group, reporting of the data, etc.) which would prevent classification of the evidence in the category of "sufficient evidence" above.

iii. Inadequate evidence of developmental or reproductive toxicity in animals. "Inadequate evidence" means that evidence does not meet the criteria of the above categories and that there can be no interpretation of the data as showing either the presence or absence of a chemical exposure-related effect.

E. Sensitization

The Commission already has issued a supplemental definition concerning sensitization, which is at 16 CFR 1500.3(c)(5). While that discussion relates to the separate category of hazardous substance referred to in the FHSA as a "strong sensitizer," the principles contained in that section will serve also as a guide to determine when a substance is toxic due to the chronic hazard of allergic sensitization.

F. Evaluation of Risk From Exposure to Substances That May Present a Chronic Hazard

1. Guidelines for Assessing Exposure—a. *Introduction.* The FHSA defines as toxic "any substance which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface," 15 U.S.C. 1261(g). Under the FHSA, a toxic substance is "hazardous" if that substance "causes personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use," 15 U.S.C. 1261(f)(1)(A). In order for a substance to be considered a hazard by this definition, it must not only have the potential to be toxic, but it must be demonstrated that (a) persons are exposed to the substance, (b) the substance can enter the body, and (c) there is a significant risk of an adverse health effect(s) associated with the handling and use of the substance. These represent, in turn: exposure, bioavailability, and risk. This section discusses the subject of exposure, and is intended to be used in the determination of significant risk of chronic toxicity of art materials or other products subject to the FHSA.

A discussion by the Office of Science Technology Assessment and Policy (OSTP) concerning the level of evidence that a chemical or product poses a carcinogenic risk to humans and the level of exposure of the consumer when the product is used is presented in the Federal Register (50 FR 10372 (March 14, 1985)). Although advances have been made in the area of modeling and monitoring exposures during the five years since this publication, many of the variables concerning the use patterns, distribution of pollutants, sources, sinks, relationships between physical parameters and market penetration of products have not been defined to a level where predictive modeling can in any sense replace well-conducted field studies. Many of the strengths and weaknesses of the approaches discussed by the OSTP remain the same today as in 1985. These approaches are discussed in the following subsections.

Three routes of exposure—inhalation, dermal absorption, and oral ingestion—will be discussed in separate subsections in the following discussion. The largest current technical effort has been driven by the recent interest in indoor air quality. Thus, inhalation is the most thoroughly investigated exposure route. Oral ingestion has been largely addressed in dietary and food additive studies, while dermal contact is largely of interest to the cosmetics industry and hence also to FDA.

Protocols exist for both oral and dermal contact for foods, drugs, and cosmetics. They include procedures for considering the form of the material being studied, the site of application (for cosmetics), and amounts potentially consumed (for food). Similarly, the form of the product as used should be taken into consideration when designing exposure studies. Using pure chemicals to assess consumer exposure and subsequent health effects when the product under consideration is a mixture, is not likely to provide an accurate reflection of exposure. For example, in assessing exposure from di-2-ethylhexylphthalate (DEHP) rather than studying pure DEHP, the staff performed experiments with actual products in order to demonstrate release of DEHP from the products' plastic matrix and transfer to either skin or saliva. Exposure studies with paint removers demonstrated that studies using methylene chloride alone, rather than a formulated paint remover, would have resulted in erroneous exposure estimates.

There are a number of procedures for assessing exposure of individuals or populations to chemicals which may cause cancer or other adverse health effects. Reasonably accurate exposure data are important in the assessment of risk. The accuracy needed can not be categorically stated since such factors as potency, concentration, and strength of evidence for toxicity of the chemical of concern are all important in defining the resources required to obtain the data necessary to perform an exposure assessment. Further, when using population estimates, the broad range of use patterns, frequency of use, diversity of products, and the variations in the types of housing where the products are used, will lead to exposure limits that

are often several-fold multiples of the predicted average exposure. Information concerning use patterns, frequency of use, definition of housing stock, and definition and market penetration of the products of interest is often lacking.

b. *Background: the three routes of exposure.*—i. Inhalation. Active interest and advances in exposure assessment have been largely driven by the current concern about indoor air quality and past activities involving occupational exposure and ambient air quality criteria and monitoring. Although exposure estimation techniques are becoming more sophisticated, there is no universally accepted minimum set of specifications for either data collection or estimation of exposure from the collected data. Generally, exposure is assessed by direct monitoring of populations, predictions of exposure, or use of surrogate data. These three approaches are briefly discussed below.

(a) *Direct monitoring* involves monitoring the general population or select segments of the population for exposure to a chemical or chemicals. Past monitoring studies have provided concentrations averaged for various periods of time and concentration measured at discrete times. Such data were obtained for carbon monoxide and nitrogen dioxide, power plant plume dispersion/reaction and concentrations of various chemicals in such locations as work places, point sources, cities, and even regions. Similar data bases do not exist for equivalent populations for residential indoor air. Examples of recent studies addressing residential air quality are: The EPA TEAM study (Wallace, 1987), the Pierce Foundation New Haven study (Stolwijk, 1983), the Gas Research Institute Texas unvented gas space heater study (Koontz, 1988), the CPSC Atlanta unvented gas space heater study (TRC, 1987), and the Harvard Six Cities Study (Spengler, 1985).

These studies provide measurements of the concentration and duration of concentration for combustion products, volatile organics, particulates, and biological materials. In addition, they provide limited real time monitoring and information concerning selected health effects information. With field monitoring studies, due to the potential for exposure to pollutants other than those monitored, a health effect associated with one of the monitored pollutants may not be accurate.

(b) *Predictions of exposure (through modeling)* to a chemical(s) can be based on physical and chemical principles, mass balance principles and mathematical models. Examples of such studies are: (1) The exposure predictions presented in various CPSC staff reports on unvented kerosene and gas space heaters; (2) the CPSC–EPA and CPSC–LBL methylene chloride exposure studies from use of paint strippers; and (3) the CPSC–EPA exposure studies of perchloroethylene from dry cleaning and other uses.

Data necessary for use in predictive modeling are often obtained from studies on products in small chambers (50 to 100 liters), large chambers (20,000 to 30,000 liters), or in research houses. The studies are usually designed for specific products. In general, protocols, although having common features, are not directly applicable to other products which may be investigated.

Often such modeling studies are based on data obtained from representative products used in room-size chambers or research houses. The distinction between a modeling study and a field monitoring study is that often the modeling relates to a specific product while a field study may only attempt to identify the pollutants and their concentrations, not their sources.

(c) *Surrogate data* (data of exposure derived from chemicals of similar structure, reactivity and volatility as the chemical of interest) are used by some investigators when no data exist for the chemical of interest. Surrogate data have not been used extensively by the Commission but have been used in some instances by EPA in pesticide exposure estimates. Surrogate data should only be used for preliminary evaluations to establish the scope of additional studies that will be needed to define exposure more accurately.

ii. Ingestion. Ingestion studies have been performed for organics and inorganics in foods. The bioaccumulation of pesticides and chlorinated compounds has been studied in shellfish and edible fish. In its "total diet studies" the FDA has provided data on the concentrations of selected chemicals in approximately 200 foods purchased in grocery stores throughout the United States. These data, in conjunction with data obtained from tissue analyses for pesticides, provide estimates of the exposure, body burden and effectiveness of regulatory programs intended to limit exposure to certain pesticides.

These studies involve direct monitoring of sources of chemicals as well as fate of the chemicals in products such as foods. Laboratory simulations have been developed to estimate exposure to chemicals on a smaller scale. These latter studies do not usually involve a living species but are based on leaching or extraction of the chemical from a product with a simulated saliva or gastric fluid. Examples of such studies are studies performed by the FDA concerning lead released from decorated glassware (Soc. Glass Decorators, 1979), CPSC's studies concerning lead released from printed paper products, and CPSC's studies of nitrosamine and DEHP released from pacifiers.

The estimation of exposure from ingestion of chemicals present in foods or consumer products is then predicted based upon estimates of use of the product and its release from the product. In the case of oral ingestion of consumer products containing chemicals, data on chemical content of the products may be known. However, the exposure directly resulting from those products must be predicted on the basis of population studies of random households inquiring into the products used and their composition.

iii. Dermal exposure. Dermal exposure involves estimating the amount of substance contacting the skin. This may involve experiments measuring the amount of material leached from a product contacting a liquid layer which interfaces with the skin, or the amount of substance which migrates from a product (in solid or liquid form) which is in contact with the skin. Parameters which must be considered include surface area of the skin contacted, duration of contact, frequency of contact, and thickness of a liquid interfacial layer. Examples of how these types of experiments might be applied to exposure assessments can be found in the Commission's exposure assessments on dioxin and arsenic leached from children's playground equipment.

More recently, *in vitro* testing using animal or human skin held in specially designed cells has allowed the rate constants of penetration of various chemicals to be determined. This approach can be performed in the laboratory and, thus, is more controlled than experiments involving live animals or humans. Examples of studies using this approach are studies of the penetration of cosmetics and topical drugs performed by the FDA, and studies of the penetration of DEHP and formaldehyde performed by the CPSC.

c. Discussion of exposure estimates. Each of the three approaches for exposure assessment described above have certain strengths and weaknesses as discussed below.

i. Inhalation.—(a) *Direct monitoring.* Direct monitoring will provide the strongest data for demonstrating and quantifying exposure and should be used when available. The data obtained from such studies represent

measurements made in actual living conditions. The effects of weather, a residence's structural characteristics and contents, and human behavior are all reflected in the data obtained. With proper monitoring protocols, various human activities, weather conditions, source use (where the source of chemical is known), and other information directly of interest can be obtained. The resulting data base will reflect measurements of actual maximum and minimum concentrations and may provide adequate information to determine the effect of various parameters which affect the ultimate exposure. Such parameters include, but are not limited to, air exchange rate, ambient-indoor temperature differences, wind speed, type of heating system, and frequency of use of the source of interest. Direct monitoring studies can be of either randomly selected populations or selected specifically to represent a segment of the population expected to be at risk of exposure.

Data from such population studies are important not only because they provide direct measurement of human exposure, but also because, when well-designed and -conducted, they provide valuable information for the development of models to predict human exposure.

(b) *Modeling.* Mathematical modeling, another approach for assessing exposure, is based on the principles of conservation of mass; these models are often called mass balance models. The models may be one compartment where the whole house or building is treated as a single volume, or two or more compartments where rooms or portions of rooms are treated as individual exposure entities.

Model development with field validation has been largely performed using single story houses in investigations of unvented space heating appliances and gas ranges and ovens. In these cases the single compartment model has described the distribution of pollutants throughout the living space (Traynor 1983). A single compartment model in a house where there are multiple rooms appears to be adequate for predicting exposure to combustion products with heating appliances (Traynor 1987). This is a result of the heat produced by the appliances which rapidly disperses the pollutant throughout the house, leading to a uniform distribution of the pollutant. The case of multistory houses is less clear. In a study by the Gas Research Institute (Gas Research Institute in press) in a split entry research house, the distribution of pollutants from unvented gas space heaters or gas ranges/ovens was uniform at or above the levels where the heater was located. When the heater was in the lower "game room" area, pollutant distributions were uniform throughout the house. However when the heater or range/oven was operated on the second level which contained the kitchen, living room, and bedrooms, the pollutant concentrations were uniform on the second level and near background on the lower level.

During these studies the central heating system was not used. Thus, the effect of the furnace fan in distributing pollutants in the house is not known. The concentrations of the reactive pollutant, nitrogen dioxide (NO_2), were nearly always higher in rooms distant from the heater than in the room where the heater was located. This effect was attributed to a combination of the reactive decay and convective transfer of pollutants within the house. Modeling pollutant concentrations in houses of three or more stories will be further complicated by the stack effect of the house itself and the more convoluted path required for the pollutant to move from room to room.

The following criteria are minimum inputs for use of mass balance models:

(1) Source strength of the pollutant-emitting product (obtained from literature and field or laboratory studies).

(2) Housing characteristics (obtained from literature or housing surveys specific to the pollutant source of interest), such as:

(a) Number and size of rooms,

(b) Level of insulation in floors, ceilings, and exterior and interior walls,

(c) Reactive decay rates if appropriate for certain pollutants,

(d) Air exchange rates for the sample being modeled,

(e) Construction characteristics of the housing sample,

(f) Occupant behavior involving the house,

(g) The number and usage of the pollutant source in the structure, and

(h) The type of central heating and air conditioning used in the house.

(3) Ambient conditions which are likely to be encountered for the population under study, such as:

(a) Ambient wind speed which can affect the infiltration rate (air exchange rate) and, thus, alter the concentration ranges predicted,

(b) Ambient temperature which is an important factor in air exchange and air distribution within a house, and

(c) Ambient surroundings that can affect the wind's and sun's effect on the house by providing shading or breaking the normal wind velocity.

All of these factors should be considered in modeling exposures.

The list of criteria needed for modeling is extensive and often the information is not available in the necessary detail to fill all cells of the model. It is often necessary to review the existing literature and use as inputs data representing the average and range of values reported. Although data from field studies of occupied housing should be used in exposure assessments, they are not always available. When field study data are available they should be used not only for the exposure assessment, but also for determining averages and distributions for the purpose of model development. Alternatively, where data are lacking, averages and ranges from laboratory chamber studies can be incorporated. Examples of such data are emission rates from unvented space heaters which have largely been determined in laboratory chambers the size of a small room. These data are often supplemented by small field studies of select populations using the appliance or product of interest. Such studies are used to confirm the laboratory-determined emission rates and to provide a limited validation of the predictive capability of the model. Examples of such studies are those performed by LBL (Traynor, 1983) and the Pierce Foundation (Stolwijk, 1983) with unvented gas and kerosene space heaters.

Exposure assessment models should be validated. The assumptions and limitations of the model, the validation process, and validation results should be described. Validation is generally done by comparing model predictions with the results of field or laboratory studies. Where possible, model validation should utilize input parameters independent of the field study house(s) being monitored for validation purposes. The model validation comparison should reflect the ability of the model to predict average, high, and low concentrations in a house.

Models have provided much of the exposure information for combustion products used by various federal agencies, both to determine the need for extensive field studies and to determine regulatory approaches. The modeling studies performed for combustion products predicted the concentrations measured in dwellings reasonably well, in large part, because the appliances under investigation produced a large amount of heat which drove the combustion products rapidly throughout

the dwellings. Thus, a relatively simple, one compartment model was suitable for assessing exposure. However, when there is no driving force to distribute the chemical of interest throughout the dwelling, *i.e.*, heat or a central ventilation system, the prediction of concentrations throughout a dwelling becomes less accurate. An example of the latter was the LBL study (Hodgson 1987) of paint removers tested in a room-size chamber and used inside dwellings to remove paint from standard panels or furniture. Until validation data from research house and field studies is obtained, models should only be relied on as preliminary estimates of exposure.

(c) *Surrogate data.* Surrogate data should be used only when data on a particular pollutant or source are sparse or unavailable. Care should be taken in interpreting surrogate data in order to minimize potential errors due to the following differences between the surrogate substance and the "real" substance of interest.

There may be differences in product composition. Linear extrapolation of pollutant concentrations based on differences in concentrations in the surrogate and "real" product are not appropriate. Matrix effects of the surrogate product may not be defined in sufficient detail to permit a valid extrapolation to another product.

Differences in the physical properties of the surrogate and the "real" substance may exist. Differences in such physical properties as vapor pressure, viscosity, and diffusion constants may be great enough to introduce substantial errors into the exposure assessment.

Finally, differences in reactivity/absorptivity may affect the ultimate emission rate and, thus, concentration measured or predicted.

In general, surrogate data should be used as a screening process to determine whether additional studies are necessary and what the parameters for those studies are.

ii. Oral ingestion. When chemicals are suspected to leach from a product, such as pacifiers or flame retardant treated sleepwear, studies designed to assess solubilization of the chemical using simulated saliva and chewing are required. If portions of the product may be swallowed, the product should be subjected to simulated gastric fluids to assess the chemical's release.

The diverse nature of consumer products precludes a standard protocol for exposure based on oral ingestion studies. Generally, each product will require specific procedures and techniques to assess exposure. However, once human factors data defining product use are available, the following criteria should be established to assess exposure:

(1) A stimulant or range of stimulants should be carefully selected to mimic the possible range of conditions which can occur in humans. Such conditions may represent full and empty stomachs, or various saliva compositions which differ during the course of the day.

(2) The mechanical action to which a product is submitted must be chosen to represent some range of realistic conditions to which a human may subject the product. This consideration should encompass the population using the product, such as infants, toddlers, young adults, and older adults.

(3) The simulation to be used to mimic the use of the product (*i.e.*, rubbing, abrasion, body area and areas in contact with the product) should be defined.

iii. Dermal exposure. Dermal exposure concerns the amount of a substance in contact with the skin over a period of time. In order to adequately define the amount of dermal exposure the following factors need to be considered: concentration of the substance in the product, migration of the substance from the product to the skin, site of application, skin surface contacted by the product (or substance), duration of exposure, and frequency of exposure. Examples of dermal exposure assessments previously performed by the Commission include those on dioxin in paper products (Babich, 1989), arsenic in wood playground equipment (Lee, 1990), and TRIS flame retardant in infant sleepwear (CPSC, 1977).

The diverse nature of consumer products and exposure scenarios precludes the development of a standard protocol for dermal exposure. The general protocols described below are given to illustrate the numerous factors which should be considered. One can envision that dermal exposure may occur by one of the following general pathways: (1) the substance is contained or bound in a solid matrix which is exposed to a liquid that contacts the skin (*e.g.*, dioxin in infant diapers, TRIS in infant sleepwear); (2) the substance is contained or bound in a solid matrix which contacts dry skin (*e.g.*, dioxin in communications paper, TRIS in infant sleepwear, arsenic in wood playground equipment); (3) the substance is dissolved in a liquid which contacts the skin (*e.g.*, dish detergent); and (4) the substance contacts the skin directly.

In pathways 1 and 2, the critical factor in assessing exposure is estimating the rate or extent of migration of the substance from the matrix to the skin. In pathway 1, migration is mediated by the liquid (*e.g.*, urine, perspiration), whereas migration in pathway 2 is unmediated. The distinction between pathways 1 and 2 may be contrived. Migration of dioxin from communications paper to the skin was modeled as unmediated migration by the Commission (Babich, 1989) and as liquid mediated migration with sebum as the liquid phase (A.D. Little, 1987). In pathway 1, migration may be described by a solid: liquid partition coefficient (K), defined by:

$$K = C(\text{solid})/C(\text{liquid})$$

where C(solid) is the concentration in the solid matrix and C(liquid) is the concentration in the liquid phase. Partition coefficients are generally measured in the laboratory. The conditions used in the laboratory should mimic the intended use. For example, for dioxin in infant diapers, fluff pulp with a known dioxin concentration was extracted with synthetic urine at 32 degrees for intervals up to twenty-four hours (NCASI, 1989).

The migration rate in pathway 2 may be determined by direct measurement (*e.g.*, Ulsamer, *et al.*, 1978).

d. *Conclusion.* Due to the multitude of consumer products and art materials, it is not possible to describe default scenarios for each product. Exposure scenarios should include customary or reasonably foreseeable use, including reasonably foreseeable accidental handling and use.

In most cases the best estimate of exposure (average exposure) is acceptable. Conservative estimates (i.e., those which may lead to overestimation of exposure, such as the upper confidence limit, "reasonable worst case," or "maximum exposed individual") are not required, but may be more appropriate in some cases. For example, conservative estimates should be used in cases where exposure data are lacking. Conservative estimates may also be useful to demonstrate that a certain exposure is not of concern. Exposure distributions are preferable to point estimates, provided that there are sufficient data for their development. In some cases, a range of exposures is appropriate, such as when the exposure distribution is bimodal.

It is important to note that exposure assessments for a single consumer product often represent only incremental additions to the total exposure that results from use of multiple products in the home. Thus, it may be useful to define what portion the incremental exposure is of the total environmental exposure. However, this determination may be difficult since data concerning other sources; and use

and duration of use patterns for a population or population segment, are often unavailable from the current base of human factors knowledge. While the focus of the guidelines is on individual products, exposures from other sources should be considered if they are known to the toxicologist.

In assessing exposure, all available data should be considered, including data from field studies, modeling studies, and studies of surrogate products. In general, field data are preferred over modeling studies, which are preferred over surrogate data. On a case by case basis, one must decide, for example, whether a good modeling study is better than a poor field study. Typically, the Commission uses both field data, when available, and model predictions. In most cases the Commission has utilized surrogate data only when there is reasonable assurance that they will accurately represent the chemical of interest.

2. Guidelines for Assessing Bioavailability

a. *Introduction.* The LHAMA directs the Commission to issue guidelines specifying criteria for determining when any customary or reasonably foreseeable use of an art material can result in a chronic hazard. This section discusses the LHAMA's directive to specify criteria for assessing bioavailability of chronically hazardous substances contained in art materials. Since the content of the guidelines can also apply to sources other than art materials, these guidelines should be considered for other products subject to the FHSA.

As explained in the previous section, bioavailability, which is concerned with the ability of a substance to be absorbed into the body, is one part of the inquiry into whether a toxic substance is "hazardous" under the FHSA. Therefore, these bioavailability guidelines will serve as part of a larger effort to outline the principles to be used in evaluating the risk resulting from exposure to materials that may present a chronic hazard.

b. *Bioavailability.*—i. *Background.* Bioavailability is a term used to indicate the extent to which a substance is absorbed by the body. The bioavailable dose can differ from the dose available for exposure (such as the amount ingested, the amount available for respiration, the amount deposited on the skin, etc.) and can also vary widely depending on the chemical nature of the substance and the route of entry into the body. For example, the estimated fraction of dietary lead absorbed by adults is only about eight percent (Rabinowitz, 1973). On the other hand, a volatile solvent, such as chloroform, whose vapors have high blood solubility can be expected to be almost completely absorbed during inhalation (Klaassen, 1980).

For purposes of these guidelines, an assessment of bioavailability will include, when necessary, the rate as well as the extent of absorption. Depending on the exposure scenario, the bioavailable dose may be directly affected by the rate at which a substance enters the body, particularly in the case of short-term inhalation and dermal exposures of slowly absorbed compounds. The rate of absorption may also be important when toxicity is related to a concentration of the toxicant above a critical level rather than the cumulative body burden.

The bioavailable dose, as defined in these guidelines, should also be distinguished from the dose of toxic substance that is delivered to its site of action. In addition to absorption, this delivered dose takes into account distribution, metabolism, and excretion. Therefore, estimation of delivered dose and its application to risk assessment cannot be addressed by bioavailability considerations alone, but requires a more complete pharmacokinetic (absorption, distribution, metabolism and elimination of substances) analysis. Use of pharmacokinetic information in the assessment of risk is addressed in the set of guidelines on risk assessment procedures.

The need to consider bioavailability in estimating the risk from use of a product containing a toxic substance arises when a difference is anticipated between the absorption characteristics of a substance to which there is human exposure and those characteristics for the substance when it is tested in animal toxicity or human epidemiological studies used to define the dose-response relationship. Some situations in which this might occur are outlined below.

ii. Physical or chemical forms of a toxic substance. If the physical or chemical form of a toxic substance in a product differs from the form present in the dose-response studies used to assess risk, the comparative bioavailability of the forms of the substance must be evaluated. This is particularly true of toxic metals which can exist as water soluble salts, water insoluble salts, alkyl compounds, and in various states of polymeric aggregation. All of these forms differ in their ability to be absorbed across biological surfaces. The bioavailability of toxic substances inhaled as particulates and aerosols will also vary based on particle size.

iii. Route of exposure. Bioavailability should be evaluated when it is anticipated that the route of human exposure to a toxic substance will differ from that used in the dose-response study. This could be a relatively common situation since the test substance is often administered orally in animal toxicity studies yet human exposure to chemicals from use of consumer products is frequently through the skin or by inhalation.

iv. Presence of other constituents. When a product contains constituents that are not accounted for during the dose-response study and that are reasonably anticipated to interfere with or enhance the absorption of a toxic substance, bioavailability must be considered. For example, the extent of dermal absorption of a compound can be influenced by the type of solvent present. Toxicity studies by the dermal route often use a vehicle that maximizes dermal absorption of the test substance. However, the dermal bioavailability of the substance might be quite different in the environment present in a consumer product.

v. Dose. Bioavailability should be considered during the exposure/risk assessment of a toxic substance if there is reason to believe that the dosing conditions used in the dose-response study would introduce a non-linearity in absorption when extrapolating to conditions encountered during human exposure. Animal toxicity and human epidemiology studies on which risk assessment is based often involve chemical exposures that are higher than exposures resulting from use of consumer products. Risk assessments usually predict toxicity at those lower doses using mathematical models that do not fully apply the biological non-linearities that can sometimes exist. In certain instances, non-linearities in absorption can influence low dose extrapolation. Some toxicants are absorbed from the gastrointestinal tract by carrier mediated transport systems [2] that may be saturated at the dose utilized in dose-response studies. Saturable metabolism (level of metabolism which cannot be exceeded) of toxic substances can produce non-linearities in bioavailability. This is particularly true following gastrointestinal absorption since the major metabolic organ in the body, the liver, receives the absorbed materials

[2] Carrier mediated transport requires the existence of a macromolecular carrier responsible for binding the substrate on one side of a biological membrane and releasing it on the other side. This process can be saturated at high doses.

via the portal circulation before the materials are available to the systemic circulation. The fraction of the applied dose absorbed as measured during dermal penetration studies is frequently less at high doses than at lower doses. Therefore, extrapolation of absorption data at high dermally applied doses without further study at lower doses could underestimate bioavailability.

vi. Other conditions. Other aspects of a dose-response study may make it inappropriate to estimate human risk without making adjustments in bioavailability, particularly if the animal model or human population under investigation does not adequately approximate the absorption characteristics anticipated in the population of concern. For example, certain metals, notably lead and cadmium, are more efficiently absorbed in the gastrointestinal tract of younger animals (and humans) than adults (Hoffmann, 1982). Thus, it is necessary to correct for this absorption difference when estimating risk to children based on a toxicity study in adult animals. In addition to age, other factors that might affect adjustments in bioavailability are animal species, sex, and strain. It may also be necessary to adjust bioavailability to reflect differences in dosing regimen. Often animal studies are conducted under conditions of repeated dosing while human exposure from use of a product may be intermittent.

vii. Special cases where bioavailability has been accounted for in exposure and risk assessments. Sometimes certain aspects of bioavailability are inherently accounted for during the assessment of either risk or exposure. Risk assessments that rely on pharmacokinetic models to account for non-linearities in delivered dose will usually have made a correction for bioavailability. Exposure assessments based on biological monitoring data, such as urinary metabolites or adducts present in the blood, will often have accounted for bioavailability due to the nature of the measurement. In these cases, it may be unnecessary to assess bioavailability separately.

c. *Guidelines for the assessment of bioavailability*—i. General strategy for assessing bioavailability. Three routes of exposure are normally encountered during use of consumer products: inhalation, ingestion, and dermal contact. Once the exposure assessment has established the routes of concern and the amount of toxic substance available to the appropriate absorptive surface (*i.e.*, respiratory tract, gastrointestinal tract, and skin), bioavailability should be addressed if any of the conditions described above requires it. This should be done for each toxic substance and each route of exposure presented by the product.

Two general approaches may be used to account for bioavailability in the process of estimating risk: a default value can be assumed for the amount of substance absorbed or a bioavailability assessment can be performed. The default value should be used when there are no adequate data which would lead to an alternative approach. The goal of the bioavailability assessment is to provide a quantitative estimate for the amount of substance absorbed into the body. There may be several acceptable measurements from which bioavailability can be determined.

Although all available data should be considered, it is usually best to use *in vivo* absorption studies for the substance of interest. *In vitro* data can often be used to supplement *in vivo* data. (With *in vivo* studies, the substance of interest is introduced into a live animal. With *in vitro* studies, the substance's effect on tissue or cells isolated from the animal is studied.) Bioavailability assessments based on *in vitro* data are acceptable if *in vivo* studies are not available, if *in vitro* data are shown to be of superior quality, or if *in vitro* data more closely approximate the exposure conditions anticipated from use of the product in question. In the absence of substance-specific absorption data, it is acceptable to use a bioavailability estimate based on the default assumption or a surrogate measurement of a related compound that is known or anticipated to be no less than the actual extent of absorption. In instances where no other acceptable data exist, a bioavailability estimate of a related compound whose bioavailability is expected to be less than that of the substance of interest, but not beyond the magnitude of reasonable experimental error, can be used. However, if a related compound has been chosen based on a surrogate measurement, it must be justified that small differences in the surrogate data will not cause the extent of absorption to be underestimated beyond reasonable acceptability limits. The acceptability limits and the conditions on their use apply in subsequent discussions of surrogate bioavailability data. These approaches are also useful when the risk is anticipated to be negligible as might occur with products containing very low concentrations of a toxicant or products whose use leads to very low human exposure. A bioavailability estimate that is known or anticipated to underestimate the extent of absorption should not be used. A qualitative assessment can sometimes assist in choosing a method to estimate the bioavailability of a substance. In cases where bioavailability is considered, exposure estimates must be adjusted for the fraction of substance absorbed relative to the dose-response study.

(a) *Default approach.* The default value for bioavailability assumes that 100 percent of a substance to which a person is exposed will be absorbed. Although the default assumption may overestimate absorption, it usually has the advantage of allowing a relatively quick and easy determination of an upper bound on risk without the need for a more time-consuming quantitative bioavailability assessment. Because exposure estimates must be adjusted for relative bioavailability, risk assessments based on the default value may still require a quantitative evaluation of the fraction absorbed under conditions of the dose-response study (see discussion below).

(b) *Bioavailability assessment.—Qualitative approach.* A qualitative assessment may be useful in choosing the final quantitative approach necessary to account for bioavailability. If a qualitative assessment can demonstrate that the bioavailability from use of a product is anticipated to be no greater than the bioavailability that would result under the conditions of the dose-response study, it is acceptable to assess risk based on the assumption that a substance is absorbed to the same extent as occurred in the dose-response study. Like the default assumption, this approach may overestimate bioavailability but could, nevertheless, provide an acceptable value with minimal time and effort.

A qualitative assessment can also justify utilizing bioavailability data for a related compound when data are not available for the substance of interest, provided all critical factors related to absorption by the route under consideration are taken into account. In this case, there must be compelling evidence to indicate that the bioavailability of the surrogate compound is no less than the substance under consideration. Because these are not quantitative determinations, data other than direct bioavailability measurements are sufficient to complete the assessment. For example, a knowledge of the relative solubilities of two forms of a toxicant may be sufficient to allow data on gastrointestinal bioavailability of the more soluble form to be used to estimate

the risk from ingestion of the less soluble form of the same substance. The type of measurements sufficient to produce a qualitative determination are route-specific and will be discussed below.

Quantitative approach. If a bioavailability assessment is needed and the default assumption is not used, then quantitative estimates for the amount absorbed must be determined. The necessary data may be available to sufficiently quantify bioavailability or the appropriate experimental studies can be conducted to generate this information. Acceptable methods for determining bioavailability depend on the route of exposure. However, there are some general considerations common to most bioavailability measurements that will be discussed here.

Bioavailability measurements from in vivo exposure. The most definitive method of determining bioavailability is to measure it directly after *in vivo* administration by the exposure routes of interest. When systemic bioavailability (the fraction of the administered dose that enters the systemic circulation) is the appropriate measure, the relative availability between exposure conditions and those of the dose-response study can be determined by a comparison of the total areas under the substance concentration in plasma versus time curve (area under the curve or AUC). This procedure estimates the amount of a substance to which a specific part of the body is exposed over time. The ratio of the AUCs can be shown to be equal to the relative extent of absorption (Gibaldi and Perrier, 1982) and can be used directly to adjust exposure estimates for calculation of risk. In cases where the toxicity of interest occurs at the site of exposure, such as effects on the skin following dermal exposure or respiratory toxicity from inhalation, systemic bioavailability is not a relevant measure; extent of absorption must be determined from the concentration in the tissue of interest.

For example, if a substance was given orally in a dose-response study and the principal route of exposure from use of a product was by inhalation, relative bioavailability can be calculated as $AUC_{inhalation}/AUC_{oral}$, provided comparable doses of the substance were administered. Mathematical accommodations can be made if different doses are given. The AUC method requires that plasma concentration of the substance be determined at several time points after dosing until at least 2 to 3 half-lives of elimination have occurred. Relative systemic bioavailability can also be determined using cumulative excretion data. This necessitates that excreta be collected from the major routes of elimination (urine, feces, expired air, etc.) until virtually all the substance has been expelled from the body. Regardless of the measure used, it is important to account for both the parent compound and its major breakdown products.

Use of radiolabeled compounds is usually the most effective way of insuring a complete accounting of the parent and its metabolites. Bioavailability measurements for at least two doses that span 1 to 2 orders of magnitude may be necessary in order to address possible non-linearities. In all situations, the doses employed should be such that the processes of absorption and metabolism (when it affects bioavailability) are not compromised. In general, bioavailability testing should conform with the EPA Good Laboratory Practice Standards (EPA, 40 CFR part 792) and applicable test standards for pharmacokinetics (EPA, 40 CFR part 798.7485).

Other data that may be used to quantitate bioavailability. Types of data other than *in vivo* measurement may be used to estimate bioavailability. Under the proper circumstances, absorption can be determined from *in vitro* preparations utilizing isolated organs. When estimating bioavailability from any *in vitro* preparation, it is important to ensure that it is truly representative of *in vivo* processes. For example, an isolated segment of intestine should not be utilized to assess absorption of a substance that also enters the body through the stomach or another part of the gastrointestinal tract. In most situations, it must also be demonstrated that the preparation was viable during the period of measurement and that those factors critical to bioavailability of a particular substance, such as specialized transport or metabolism, approximate the *in vivo* condition. Uptake studies using isolated cell systems, or subcellular fractions where cellular organization has been disrupted, are usually not sufficiently representative of the *in vivo* situation.

In certain defined circumstances, use of surrogate data to estimate bioavailability is acceptable. For example, the amount of substance absorbed from ingestion of a solid material can sometimes be estimated by measuring its solubility in media designed to mimic the gastrointestinal environment. Blood:gas partitioning (the relative amount in blood versus the amount in air) can sometimes assist in determining systemic bioavailability following inhalation of gases and vapors. The respirable fraction of dust and aerosols is sometimes an adequate estimate of that portion available for absorption through the alveoli of the lung. In order to use surrogate data, the test method used must accurately reflect the absorption process it is substituting for, and any results must be reproducible. Data that overestimate the bioavailability are also acceptable, as noted previously.

Physiologically based models can also provide estimates of absorption. These models mathematically describe absorption in terms of physiological and biochemical parameters, such as, ventilation rate, blood flow, partition coefficients, and absorption rate constants. Physiological models have the advantage of being able to predict systemic or tissue bioavailability under different conditions, but they frequently require access to large amounts of input data. Model-dependent parameters should always be identified and the methods used to determine their values clearly stated. Like other methods used to generate surrogate data, models must be validated to ensure that they adequately estimate the particular measurement of interest.

(c) *Adjusting exposure estimates for bioavailability.* Route-specific exposure resulting from a particular product use can be expressed as the amount of substance to which one is exposed per body weight per day. This average daily dose can then be multiplied by a relative bioavailability ratio to give the amount of substance that contributes to the body burden for a particular situation. The relative bioavailability ratio determined by the bioavailability assessment is defined as the fraction of a substance absorbed from a specified exposure as a result of product use divided by the fraction absorbed during the dose-response study. Exposure estimates must be adjusted by the relative bioavailability ratio whenever exposure to a substance from product use leads to the conditions outlined in subsection b. above. This ratio takes a value of 1 when the bioavailability is assumed to be approximated by the dose-response study itself. If a use scenario involves multiple routes of exposure, the route-specific average daily doses may be summed to get the total average daily dose for a particular use scenario.

ii. Routes of exposure. The predominant routes of exposure encountered during use of consumer products are ingestion, inhalation, and dermal contact. The biological surfaces that function as bioavailability barriers

are different for each exposure route and, thus, the factors that control and the methodologies used to measure absorption can vary. This section will discuss the critical features that must be considered in determining absorption across the gastrointestinal tract (ingestion), respiratory tract (inhalation), and skin (dermal contact).

(a) Gastrointestinal tract.—Transport characteristics. The gastrointestinal tract is the site of potential absorption for ingested substances. Although, in principle, absorption can take place along the entire length of the gastrointestinal tract from mouth to rectum, most absorption takes place in the stomach and small intestine where larger surface areas, longer residence times, and higher perfusion rates are most conducive to transport across the mucosal barrier. The most common mechanism by which toxicants are absorbed across the gastrointestinal tract is by passive transport [3] through the absorptive cells. Absorption by this mechanism is greatest for small uncharged lipid soluble molecules with adequate aqueous diffusivity. In fact, for a series of non-electrolytes of similar molecular size, gastrointestinal absorption can be shown, in general, to be proportional to lipid solubility as measured by oil:water partition coefficients. Ionizable compounds such as organic acids and bases are not well absorbed in their ionized form, and the extent and rate of absorption will be governed by the pH at the absorption site and the pKa of the chemical. Thus, organic acids are likely to be better absorbed in the acidic environment of the stomach, while organic bases would be expected to be better absorbed in the more basic pH of the intestine. While lipid soluble compounds diffuse through the gastrointestinal cells, small water soluble compounds are capable of diffusing through aqueous pores located at the junctions of the intestinal epithelial cells. This is a major mechanism by which water and small electrolytes, such as potassium and sodium ions, penetrate the gastrointestinal tract. Other water soluble chemicals with a molecular weight below about 200 daltons have also been shown to be absorbed this way (Schanker, 1962).

Several more specialized transport systems exist in the gastrointestinal tract that can be responsible for absorption of selected substances. Some chemicals are transported by a carrier mediated mechanism. This type of transport is primarily responsible for absorption of some nutrients and endogenous substances, but sometimes non-essential chemicals, including metals, such as lead and aluminum, and several quaternary ammonium compounds, are capable of utilizing these systems. Intestinal absorption of large macromolecules (10,000–60,000 daltons) have been documented in man and experimental animals. This is believed to occur by pinocytosis.[4] Particles up to 5–8 micrometers (um) in diameter can be absorbed by phagocytosis [3] (Aungst and Shen, 1986). However, the extent of absorption by pinocytosis and phagocytosis is generally low. Gastrointestinal absorption of charged substances of high molecular weight is particularly poor.

Physiological and physicochemical factors. Aside from the transport characteristics, there are several physicochemical, biochemical, and physiological factors that can influence gastrointestinal absorption and systemic bioavailability. The nature of a substance can sometimes be substantially altered during the absorption process: degradation can occur in the acid environment of the stomach; a toxicant can be altered by the action of digestive enzymes or the bacterial flora present in the intestines; once absorbed, some chemicals can undergo extensive metabolism in the liver before reaching the systemic circulation.

Most substances must be solubilized before absorption can take place. The rate and extent of dissolution can often limit the rate of absorption of a chemical ingested as a solid material. A key determinant of dissolution of solid material, as well as absorption of complex mixtures, is aqueous solubility. Absorption of some substances can be changed by formation of insoluble salts or molecular complexes. Dissolution of a compound in a solid matrix is influenced by particle size: Smaller particles are more easily absorbed than large particles because of their greater surface area. Sometimes the way in which a substance is formulated can have profound effects on gastrointestinal absorption. Lipid soluble substances administered in oily vehicles are often absorbed directly into the blood through the lymphatics bypassing the liver. The result could be a significant increase in systemic bioavailability if the substance is known to undergo extensive hepatic metabolism. Highly viscous suspensions can affect absorption by slowing dissolution of a substance and delaying gastric emptying.

Physiological factors must be considered when assessing gastrointestinal bioavailability. Delayed gastric emptying caused by a test substance or its vehicle can affect absorption particularly in the case of acid-labile (*i.e.*, decomposes in the presence of acid) compounds or situations where acidity influences dissolution. Gastrointestinal motility can affect absorption by altering the time spent at the site of absorption. This is critical for compounds whose bioavailability is limited by the amount of time they reside in the intestine. The gastrointestinal absorption of some substances is known to be age dependent: the absorption of many metals such as cadmium, iron, mercury, lead, and zinc is highest in newborns and decreases with age (Hoffmann, 1982).

Physicochemical properties can sometimes indirectly aid in the determination of bioavailability estimates. When a chemical is ingested as a solid material, measurements of solubility in media that mimic the gastrointestinal environment may be used to estimate absorption, assuming certain conditions are met. Use of solubility measurements as an estimate of bioavailability implicitly assumes that absorption of the soluble material is known. Other assumptions about absorption are acceptable provided that the actual extent of absorption will not be underestimated. It must be shown that the test method under which solubility is measured will not lead to a lower solubility than is expected to occur following ingestion. This requires that the surrogate method be validated against the appropriate *in vivo* models for the substance of interest, the type of material for which it is present, and its dose range.

Relative solubilities, pKa's and oil:water partition coefficients can also be utilized to justify using gastrointestinal bioavailability data for a related compound. A chosen surrogate compound should never be expected to have a lower bioavailability than the compound of interest. Absorption of a more soluble form of a toxicant should never be estimated using data from a less soluble form of the same toxicant. Absorption of organic acids should never be estimated using data from a related acid with a lower pKa. On the other hand, bioavailability of organic bases should never be estimated from a

[3] Passive transport refers to simple diffusion of a substance from one compartment to another controlled by a diffusion coefficient and the concentration or electrochemical gradient across the membrane.

[4] Pinocytosis and phagocytosis refer to transport processes by which substances are engulfed by the cell membrane.

related base with a higher pKa. The oil:water partition coefficient of the surrogate substance should never be lower than the compound under consideration. In these cases, it is essential that other factors critical to bioavailability, such as transport mechanism, molecular weight, first pass metabolism, and physiological effects do not cause the bioavailability of the surrogate compound to be less than the substance of interest.

(b) Respiratory tract: Factors that affect absorption from the respiratory system. Chemicals that are absorbed through the respiratory tract are gases, such as, carbon dioxide or nitrogen dioxide; vapors of volatile liquids, such as, benzene or methylene chloride; and aerosols, such as, silica, asbestos, and other dusts, smokes, fogs or mists. Aerosol deposition and the efficiency of absorption is dependent on particle size and charge. The majority of aerosol particles with a mass median aerodynamic diameter ("MMAD") greater than 5 um are deposited in the nasopharyngeal region of the respiratory tract following nasal breathing. The particles are usually trapped in the thick mucus blanket of the nasal surface and are rapidly removed by either mucociliary clearance,[5] sneezing, or nose blowing. Much of this particulate matter is made available to the gastrointestinal tract after swallowing of the secreta. As nasal breathing becomes augmented by mouth breathing, which might occur during exercise or periods of nasal blockage, nasopharyngeal deposition is reduced while both the fraction and size of particles reaching the deeper regions of the respiratory tract are enhanced. Some sufficiently soluble aerosols can dissolve in the mucus and be absorbed through the epithelium of the nasopharyngeal region into the blood.

Particles with a MMAD in the range of 2 to 5 um are increasingly deposited in the tracheobronchial region of the respiratory tract following nasal breathing. These are also cleared by the upward movement of the mucus layer lining this portion of the respiratory tract. However, the mucus is generally thinner and the clearance times longer, particularly in the terminal bronchiolar regions of the lung, allowing for greater opportunity of being absorbed across the epithelial cells into the blood. Coughing and sneezing can result in more rapid movement of particulate matter from the larger airways to the glottis to be swallowed.

Particles with diameters around 5 um also begin to reach the alveolus of the lung during nasal breathing; this region becomes the major site of deposition for particles with diameters less than 2 um. Lipid soluble aerosols are very readily absorbed from this zone of the respiratory tract due to the large surface area, high blood flow, and thin diffusion barriers. Because of the relatively inefficient clearance mechanisms available in the alveoli, insoluble particles can remain for long periods until they are either removed by the bronchial mucociliary system, phagocytysed by alveolar macrophages, cleared by lymphatic drainage, or slowly undergo dissolution and vascular removal. The long residence times of particulates deposited in the inner regions of the respiratory tract, combined with the relative ease of diffusion across the alveolar membranes, make the lung a significant site of absorption for those substances that adsorb on the surface of small aerosols. Inhaled particles less than 1 um in diameter can be expected to reach the deepest regions of the lung easily. However, the total deposition/retention of these smaller particles in the respiratory system is generally less since they can be exhaled. Recent data using nasal casts of humans and experimental animals suggest that ultrafine aerosols less than 0.2 um in diameter become increasingly deposited in the nasopharyngeal region of the respiratory tract. Other particle characteristics such as density, shape, and hygroscopicity [6] may influence the site of deposition and absorption.

The uptake of gases and vapors can occur throughout the respiratory system. The predominant mechanism for most gases is passive diffusion driven by the higher concentration in the inspired air relative to the tissue and blood. Aqueous soluble gases tend to be taken up by the nasopharyngeal region and upper airways. A greater percentage of the less water soluble gases reach the lower airways and alveolar region of the lung where absorption into the systemic blood occurs much more readily. Once in the alveoli, the amount of a gaseous substance that enters the blood is controlled not only by its concentration in the inspired air, but also by its solubility in blood, pulmonary ventilation, and blood flow. As one continues to breathe a gas or vapor at a constant tension, a steady state concentration in the blood will eventually be achieved. The time needed for a gas to reach steady-state is primarily a function of its solubility in blood, which is characterized by a blood:gas partition coefficient defined as the ratio of the concentration of dissolved gas in the blood to that in the gas phase at equilibrium.

A highly soluble gas with a large partition coefficient will be almost completely transferred to the blood with each inspiration, but the time needed to reach steady-state may be several hours. On the other hand, only a small fraction of a gas with low blood solubility will be absorbed into the blood and saturation may be achieved more quickly. Other factors will influence the ability of a gas to be absorbed in the blood: Time to steady-state will be more prolonged for gases that are highly lipid-soluble and can be stored in body fat; insoluble gases that are rapidly cleared by metabolism will also be absorbed to a greater extent than a gas of similar solubility that is not metabolized; an increase in pulmonary ventilation will often increase the absorption of a highly soluble gas, while an increase in pulmonary blood flow can increase the absorption of an insoluble gas; some carrier mediated or other specialized transport systems are known to exist in the respiratory tract, but are uncommon.

Other considerations may affect absorption from the respiratory tract. Inhaled substances that alter mucociliary flow, cause bronchconstriction, or directly damage the respiratory epithelium can significantly influence the bioavailability from this route of exposure. Although the metabolic capability of the lung is generally more limited than that of the liver, certain selected substances may undergo extensive pulmonary metabolism that could result in reduced systemic bioavailability. A more detailed discussion of the factors that determine the bioavailable dose following inhalation can be found in the EPA Interim Guidelines for Development of Inhalation Reference Doses (EPA, 1989).

The determination of administered dose from inhalation studies is more complex than with other routes since it is dependent on duration of exposure, respiratory rate and tidal volume as well as concentration. It is best for *in vivo* respiratory measurents to be done by plethysmography, but in its absence, appropriate values for the particular species of experimental animal may be assumed based on literature values.

[5] Mucociliary clearance refers to a mechanism by which particulates and bacteria are entrapped in a layer of mucus lining the respiratory tract and swept upward out of the system by the movement of small hairs called cilia attached to the epithelial cells of the tracheobronchial and nasal regions.

[6] Hygroscopicity refers to the ability of particles to accumulate moisture.

Administered dose calculations from experimental animals must be defined in terms of an equivalent human dose. This means that the airborne concentration has to be adjusted to reflect differences in exposure duration and breathing rate between experimental conditions and humans. The default human breathing rate during typical product use is assumed to be 20 cubic meters per day. This produces a default alveolar ventilation rate of 13.4 cubic meters per day since only a fraction of the air breathed is available for gas exchange. Appropriate ventilation rates for a number of animal species have been documented (EPA, 1988). If the test material is an aerosol, particle size distribution needs to be determined as the mass median aerodynamic diameter (MMAD). For insoluble aerosols, the amount deposited in the various regions of the lung can be estimated from the aerosol size distribution, deposition efficiency, and lung surface area. Adjustments can be made to account for differences in aerosol deposition between animals and humans (Jurabek, *et al.*, 1989).

Absorption by the respiratory tract can also be predicted using physiologically based models. These can be developed to estimate blood concentration over time resulting from inhalation of a substance or doses reaching different sites of the respiratory tract. The accuracy of these models depends on precise values for a number of physiological (ventilation rate, blood flow, airway diameter, etc.), biochemical (metabolic rates), and physiochemical (blood:gas partition, diffusion coefficients, etc.) parameters. All models should be adequately validated before being used in assessing bioavailability.

Certain surrogate data may be used to assist in determining bioavailability estimates following inhalation. Aerosol/dust particulates with a MMAD less than 10 um can sometimes be used as an estimate of that fraction available for absorption across the alveolar region of the lung. Studies indicate that only a very small fraction (<10%) of aerosols greater than this size reach the respirable region even with ventilation rates that occur during moderate to heavy exercise (Miller, *et al.*, 1988). Although bioavailability from alveolar deposition of aerosols greater than 10 um may be eliminated from consideration, potential absorption of these particulates from other portions of the respiratory tract or from gastrointestinal exposure as a result of mucociliary clearance must be evaluated.

Blood:gas partition coefficients for gases and vapors can be utilized to justify the substitution of respiratory bioavailability data from a related compound, provided certain criteria are met. The blood:gas coefficient of the surrogate compound must not be less than the compound under consideration. In addition, it must be shown that other factors that control transport from the respiratory tract such as metabolism, clearance, tissue distribution, and uptake from other regions of the respiratory tract cannot be expected to cause absorption of the surrogate to be less than that of the substance of interest.

(c) Skin: permeability characteristics. The skin serves as a relatively impermeable barrier to many chemical agents. In contrast to the gastrointestinal tract and lung in which a chemical must only pass through two cells to reach the blood, the skin has multiple cell layers that must be crossed before systemic absorption takes place. The rate-limiting step in this process is usually diffusion across the stratum corneum, the outermost densely packed layer of keratinized epidermal cells. The stratum corneum of different regions of the body will vary in thickness and diffusivity, and will be reflected in different dermal permeabilities. For example, the palms and soles are much less permeable than other skin areas because of their very thick outer layer of skin. Chemicals diffuse much more readily across the inner epidermis and dermis than the stratum corneum. Some chemicals may be partially absorbed through the cells of the sweat glands and hair follicles. However, because the cross sectional area occupied by these structures in human skin is only 0.1 to 1 percent of that occupied by the epidermis, this route of absorption is unlikely to play a major role for most substances.

Absorption from the skin is believed to occur by passive diffusion. The overriding determinants for the rate of percutaneous absorption are, therefore, the concentration gradients from skin surface to blood and the permeability of the penetrant for the stratum corneum. In addition to skin thickness and membrane diffusivity, dermal permeability is controlled by molecular size and partitioning between the stratum corneum and the vehicle in which the penetrant is present. Except for some extremely nonpolar compounds, the permeability constants for many substances in aqueous solutions have been shown to correlate well with their lipid solubility as measured by the octanol:water partition coefficient, provided their diffusivity does not greatly vary. The correlation is not as strong for the highly nonpolar compounds because the transfer of chemical out of the stratum corneum into the inner epidermis can become rate-limiting. This could possibly lead to an overestimation of dermal permeability based on the octanol:water partition coefficient. The degree of polarity can influence the diffusivity of a substance in the stratum corneum. Very polar compounds appear capable of partially diffusing through the outer surface of protein filaments, while the less polar molecules must exclusively dissolve in, and diffuse through, the lipid matrix between the protein filaments. These differences in molecular mechanism can lead to quantitative differences in the diffusion coefficient among substances. Although small moderately lipid soluble molecules appear to be best absorbed from the skin, larger molecular weight and/or ionized substances will usually be absorbed to a lesser extent. More information on how physicochemical properties influence dermal absorption can be found in the EPA Guidance for Conducting Dermal Exposure Assessments (EPA, 1992).

The vehicle in which the substance of interest is applied to the skin can affect dermal absorption in several ways. A vehicle may improve skin absorption by increasing solubility, thus, providing a greater concentration gradient for diffusion. The vehicle can increase or decrease the partitioning of the penetrant in the stratum corneum, thereby altering absorption. Some vehicles such as dimethylsulfoxide, and certain lipid extraction solvents and detergents, can accelerate dermal penetration by altering the diffusivity of the dermal barrier. This can occur by chemically destroying the integrity of the stratum corneum, either by functioning as a swelling agent, removing lipid, or altering the conformational structure of the cell layer.

A number of other factors might affect dermal bioavailability. The rate of absorption is directly proportional to the amount of surface area contacted by the penetrant: a toxicant applied over a large area of skin will be absorbed faster than an equal amount over a smaller area. Diffusion across the skin increases exponentially with rising temperature. Skin hydration affects percutaneous absorption by altering the diffusivity and thickness of the stratum corneum; dehydration can decrease permeability by as much as tenfold (Klassen, 1980). Disease or damage to

the stratum corneum can cause an abrupt increase in percutaneous absorption. Like the respiratory tract, metabolism of certain chemicals by cells in the inner epidermis may significantly decrease the bioavailability from skin. Binding of penetrant within the different cell layers may also limit bioavailability. Volatility, chemical instability, and pH of the vehicle may alter the amount of toxicant in a form available for absorption. Finally, variability in skin permeability exists among species. Good models for human skin are dependent on the compound of interest; pig and monkey skin generally appear to share the greatest similarity to human skin in terms of percutaneous absorption, but skin from other animals may also be adequate. Human skin may also be available.

Percutaneous absorption can be estimated with physiologically based models. These use physiochemical, biochemical, and physiological data, such as, diffusion and partition coefficients, molecular weight, clearance, and blood flow to predict bioavailability. The parameters used as input to the model should be experimentally determined by legitimate methods and the values being estimated by the model should be appropriately validated.

Octanol: Vehicle partition coefficients can sometimes be utilized to justify using dermal bioavailability data from a related compound. The chosen surrogate must not have a partition coefficient lower than the substance of interest. Other factors that influence bioavailability, such as membrane diffusivity and skin metabolism, also should not be expected to cause the absorption of the surrogate to be less than the compound under consideration. Since dermal absorption data are often available as an experimentally determined or a mathematically derived (based on surrogate measurements) permeability constant when the skin contact is with a liquid, this measurement needs to be converted into the absorbed dose. This can be determined by multiplying the permeability constant (cm/min) by the concentration of the chemical in the medium contacting the skin, the exposed surface area (square centimeters) and the duration of exposure (min).

3. Risk Assessment Guidelines.—a. *Introduction.* The purpose of this section is to describe the procedures to be used when estimating risk for substances which are defined as toxic by nature of their carcinogenicity. Such risks are used in conjunction with exposure information to determine whether an acceptable daily intake (ADI) has been exceeded, as described in the section concerning that subject. As explained in that section, the process of quantitative risk assessment will not be applied to other chronic endpoints (reproductive/developmental effects and neurotoxicological effects) at this time. Thus, this section will only deal with carcinogenic risk assessment.

Although these guidelines will be fairly specific, further information on the rationale behind some of the assumptions, examples of how the guidelines are applied, and examples of the application of pharmacokinetics can be found in the Commission risk assessments on methylene chloride (dichloromethane) and formaldehyde (M.S. Cohn, Inhaled methylene chloride unit carcinogenic risk assessment, June, 1985; M.S. Cohn, Estimated carcinogenic risks due to exposure to formaldehyde released from pressed wood products, February, 1986; M.S. Cohn, Updated risk assessment for methylene chloride (dichloromethane), June 1987).

b. Guidelines for carcinogenic risk assessment.—i. Selection of data upon which risk is based. For a given carcinogenic substance, the data used will be obtained from those studies used to define the substance as "toxic" by virtue of its carcinogenicity. Among these, the study leading to the highest risk should normally be used. However, other factors may be considered in the choice of the study. For example, a study with three administered doses, showing a dose-response relationship, can be given more weight than a study in the same species/strain with a single administered dose. Similarly, a study with the same route of exposure as that anticipated for human use of the product under consideration can be given more weight than a study that uses the same species/strain, but uses a different route of exposure. If both sexes in the study respond significantly, they can be combined before risk analysis if the responses are similar (as done in the case of formaldehyde). Alternatively, the risks for each sex can be determined individually and then averaged for the final estimate (as done in the case of methylene chloride). If there is more than one significantly responding endpoint, the risks for each are determined individually and then added for the final estimate. See the risk assessments on methylene chloride referenced above for an example of this treatment.

ii. High-to-low dose extrapolation. The multistage model (Global83 or later version) is used in all cases unless a convincing argument can be made for an alternative model such as one addressing a distribution of thresholds. Linearity at low dose is always the default assumption, in light of the high probability that the action of any carcinogen will interact with background cancer processes and environmental agents, as opposed to acting independently. Upon request, a copy of Global83 that will run on a personal computer is available without charge from the Commission.

The risk will be based on the maximum likelihood estimate from the multistage model, unless the maximum likelihood estimate is not linear at low dose (which happens when the first-order coefficient, q_1, is zero). In such a case, the 95% upper confidence limit on risk (*i.e.*, the 95% lower confidence limit on dose) should be used. In the example risk assessments cited above, the maximum likelihood estimate was used in the case of methylene chloride and the upper confidence limit on risk was used in the case of formaldehyde.

Modification of doses put into the multistage model may be made if sufficient pharmacokinetic information is available. See the above referenced risk assessments on methylene chloride for an example of how such information can be used to account for nonlinearities in the dose-response curve due to pharmacokinetic influences.

iii. Species to species extrapolation. For systemic carcinogens, that is, those that exert an effect remote from the site of contact, a "surface area" correction will be used if estimates of human risk are made based on animal data. At present, this correction is a factor derived from dividing the assumed human weight (usually 70 kg) by the average animal weight during the study, and taking that to the ⅓ power. On a miligram per kilogram per day (mg/kg/day) basis, the human is assumed to be more sensitive than the animal by this factor. See the risk assessments on methylene chloride for an example of this approach. There is the possibility that this factor may be changed, using the ¼ power instead of the ⅓ power, as part of a unified Federal regulatory approach. If such an approach is adopted, it will apply here.

In cases where the concentration is expressed as parts per million (such as, in air or in diet) and the carcinogen acts at the site of contact (such as, nasal passages or the lung), species may be assumed to be of equivalent sensitivity on such a basis. In other words, humans and animals exposed to the same concentration (in parts per million) in air or diet for the same proportion of lifetime are assumed to be equally

sensitive. See the risk assessment on formaldehyde for an example of this approach.

At this time, pharmacokinetics should not be used to adjust for differences between species in sensitivity to a carcinogen; briefly, this is because information on sensitivity of various species to a "target" dose is not currently available. The rationale for this decision is explained in depth in the risk assessment for methylene chloride.

iv. Route to route extrapolation. If no experimental study having the same route of exposure as that anticipated for human use of a substance is available, a study by another route of exposure is used. In such cases, pharmacokinetic methods may be used if sufficient data are available, or methods described in the bioavailability section may be used. The less information available, however, the more one has to rely on default assumptions (as discussed in the bioavailability section).

v. Scenario extrapolation. Where exposure scenarios are different from those used in the underlying study upon which estimates of risk are based, proportionality should be applied. For example, if an experimental study is performed under conditions of exposure for six hours a day, five days a week for lifetime, then the risk for a single hour of exposure is the risk from the experimental study divided by a factor of: 6 (hours/day exposure) × 5 (days/week) × 52 (weeks/year) × 70 (assuming a 70-year lifetime). If pharmacokinetic methods are used to adjust for risks at high versus low exposure levels, one must be careful not to combine level-time measures (such as in calculating a lifetime average daily dose) without taking the non-linearity into account. Where such pharmacokinetic information is available, it may be used to adjust scenario extrapolations. For example, two uninterrupted days of exposure may lead to a different time versus concentration (area under the curve) estimate than two interrupted days of exposure, due to factors such as incomplete elimination of the substance after twenty-four hours, saturation of uptake processes, or saturation of metabolic processes.

4. Acceptable Risks to Children and Adults

a. *Introduction.* Under the LHAMA, the Commission is required to develop a number of criteria to be used in the determination of whether an art material is to be labeled. Two of these are addressed here, namely, (1) "criteria for determining when art materials may produce chronic adverse health effects in children and criteria for determining when art materials may produce such health effects in adults," with the added provision that "where appropriate, criteria used for assessing risks to children may be the same as those used for adults," and (2) "criteria for determining daily intake levels for chronically hazardous substances contained in art materials."

The first of these two criteria, effects in children and effects in adults, is addressed in this section. The second, criteria for acceptable daily intake, consists of two general parts: Guidelines for determination of the quantitative risk estimated to be incurred from use of an art material containing a toxic substance, and whether or not this risk is acceptable. The first general part is addressed in other sections regarding whether or not a substance is toxic, how exposure is assessed, and how risk is estimated. The second general part, what risk is acceptable, will be addressed here. This discussion is intended to address the issue of acceptable risk with regard to all products subject to the FHSA, not just art materials.

The reasons for the inclusion of these two particular elements (risks to children and adults, and whether such risks are acceptable) in this section become clear when one considers that hazard, as well as risk, cannot normally be distinguished relative to age of the person exposed. It would be extremely rare, if at all, that a case could be made that a specific chronic hazard would apply only to children and not to adults, or vice-versa. For cancer and chronic neurotoxicological effects, hazard identification is normally based on long-term studies in animals or humans, and unless there is some rare phenomenon indicating otherwise, both adults and children would be expected to be susceptible to substances causing such effects. Similarly, exposure of an adult or child to a reproductive toxicant could lead to effects in eventual offspring. A special case is that in which a substance has an effect only during pregnancy—a child exposed to such a substance would not be at risk, but exposure to a pregnant adult could affect the unborn child.

Although children may be more susceptible to the effects of chronic toxicants, current methodologies for carcinogenic or other chronic hazard risk assessment are usually unable to distinguish between risk to children and adults for most substances. This is because (1) data do not usually exist which relate ultimate risk to age at first exposure to a substance, and (2) in the absence of such data, the basic methodologies used for risk assessment have not developed to the point where such projections can be made. Such an endeavor may be further confounded by scenarios where exposure to a substance in childhood may lead to manifestation of a disease in adulthood. Of course, there are rare occasions when data have been available to allow distinction of risks relative to age of exposure, such as the methodology applied for the estimation of risk of mesothelioma due to exposure to asbestos. In this case, there are epidemiological data relating risks observed (after a lengthy period of followup) to the age at which members of the group were first exposed.

Since currently available hazard and risk assessment methods are unable to distinguish susceptibility of children and adults in most situations, the procedures for risk assessment and determination of acceptable daily intake will apply to both children and adults. Thus, the two subjects (children and adult hazard/risk, and acceptable risk) are discussed together in this section.

b. *Acceptable daily intake (ADI) based on acceptable risk.* As mentioned above, the concept of acceptable daily intake (ADI) for a substance depends upon the projected exposure to users of a product (and possibly others affected by the product) and the estimated risks at such exposures. Thus, for any specific product the ADI of a constituent hazardous substance is defined as that exposure which leads to or is below an "acceptable risk." The recommended value of such a risk is explored below.

1. ADI for carcinogens. Although no universal figure exists, several reviewers have observed that Federal agencies, when setting a value of acceptable risk to the public for carcinogens, have often used the figure of one in a million or less. A one in a million risk means that when exposure to an agent of concern occurs, the exposed individual has an estimated additional one chance in a million during his or her lifetime of developing the deleterious effect, such as cancer. The exposure scenario being evaluated can be one use, one year's use, "normal product utility," or anticipated use over a lifetime, depending on the nature of the situation being addressed. Thus, the choice of the exposure situation evaluated is important to the concept of what risk is "acceptable." The greater the exposure, the higher the risk. Risk can be expressed in terms of exposure. For example, risk can be expressed as a risk of one in a million of developing cancer from a certain level of radon measured in a house, if the person

exposed lives in the house for a lifetime. Alternatively, risk can be expressed as lifetime risk—eating an apple treated with a pesticide every day for an entire lifetime results in a certain risk of cancer.

Federal agencies have wrestled with the notion of "acceptable risk" for many years. The FDA in 1977 (42 FR 54148), and in 1979 (44 FR 17075), concluded that a lifetime risk of below one in a million imposes no additional risk of cancer to the public. The latter **Federal Register** notice dealt with diethylstilbestrol (DES). Since the industry was unable to show that use of DES led to risks of less than one in a million, DES was banned (Marraro, 1982). EPA has considered risks in the area of one in a million to one in 100,000 as a value for "acceptable risk," although other values have certainly been considered (Lave, 1985). The range reflects the attitude that, although the line for a specific regulatory action on a substance might normally be drawn at one in a million, there is flexibility if the benefits of the particular substance drive the definition of "acceptable risk" to a higher value. Industry has also noted the one in a million value. Mieure (1984) of Monsanto Company has stated that risks less than one in a million "are not normally considered relevant for regulatory consideration; FDA, OSHA, and EPA have all stated that substances having risks below one in a million ought not be subjected to regulation."

The Commission has also acted to require labeling at estimated risks on the order of one in a million for a carcinogen. In the case of methylene chloride, some 30 products containing this compound were identified and evaluated in terms of estimated individual risks. By and large, those products having estimated risks of over one in a million were subject to a labeling requirement under an enforcement policy, and those under one in a million were exempt from this requirement. Additionally, the Commission took an action to minimize the amount of DEHP allowed in baby pacifiers when the maximum estimated risks were within the range of one to ten in a million.

The above discussion gives examples of past, present, and proposed definitions of "acceptable risk" used by Federal regulatory agencies that center around the figure of one in a million. While the discussion does not give examples of the many other figures that have also been considered or proposed, the use of one in a million has been most prominent and also has the most precedent in the case of actions taken by the Commission and other agencies for carcinogens. Other chronic endpoints (reproductive effects and neurotoxicity) should receive a similar level of concern. Therefore, for purposes of the LHAMA (and for other products subject to the FHSA), the maximum ADI under the guidelines is that exposure of a toxic (by virtue of its carcinogenicity) substance estimated to lead to a lifetime excess risk of one in a million. The term "exposure," as used in the guidelines, refers to the anticipated exposure from normal lifetime use of the product, including use by artists, art teachers, and art students. The assessment of exposure is covered in the section on exposure in these guidelines.

ii. ADI for neurotoxicological and developmental/reproductive agents. As mentioned in the section on risk assessment, no numerical risk assessment method for neurotoxicological or developmental/reproductive agents will be specified at this time. Although other Federal agencies such as EPA are developing and considering such methods for these types of chronic agents, the development is still ongoing, and they are not ready for implementation in guidelines such as these. When implementation is feasible, the Commission will specify appropriate amendments to these guidelines.

Therefore, as an alternative, a safety factor approach is specified for handling neurotoxicological or developmental/reproductive agents. Safety factors have been used extensively in the past for non-carcinogenic substances, and even for carcinogens as late as the early 1970's. Typically, a factor of ten is applied to account for potential differences in sensitivity between humans and animals, and another factor of ten is applied to account for differences in sensitivity among humans (Hutt, 1985).

Using the safety factor approach, the ADI under the guidelines is the following. If the hazard is ascertained from human data, such as that derived from epidemiological studies, a safety factor of ten will be applied to the lowest no observed effect level ("NOEL") seen among the relevant studies. For each study, the NOEL is considered to be the highest experimental exposure or dose level at and below which no significant response is observed (presumably, the next higher experimental point reflects a significant, positive response). The ADI is then tenfold less than the lowest (among the relevant studies) of these doses or exposures. If the hazard is ascertained from animal data, the ADI is one hundredfold less than the lowest NOEL.

The above concepts require some clarification. First, in the event that the only study or studies available have significantly positive responses at all levels tested (for example, only two single-point studies are available), a NOEL cannot be determined. Therefore, in such cases, the safety factor used to determine ADI will be applied to the lowest exposure or dose yielding positive results, known as the lowest observed effect level ("LOEL"). The safety factor will include an additional factor of ten (*i.e.*, ADI's of 100 and 1000 below the LOEL for situations based on human and animal data, respectively) to account for the probability that a response would occur at a lower dose or exposure.

Second, the NOEL (or LOEL) and ADI reflect daily dose levels, that is, the NOEL (or LOEL) is calculated in terms of amount per day experienced by the animals or humans under study, and the safety factor is applied to that number to determine ADI. When a specific art material (or other material subject to the FHSA) containing a toxic substance is used, if the daily exposure during use (with use, again, referring to anticipated use pattern(s)) exceeds the ADI, the product should be labeled according to provisions of the LHAMA and the FHSA.

Third, where only specific populations are susceptible, the product is still subject to the provisions of the LHAMA and the FHSA, although any labeling would identify such populations. For example, if a developmental toxicant acts only during pregnancy, this quality would be so noted on the labeling.

VII. The Supplemental Definition of Toxic

A. The Existing Statutory and Regulatory Scheme

Section 2(g) of the FHSA defines the term "toxic" very broadly as "any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface." 15 U.S.C. 1261(g). This broad statutory definition covers both acute and chronic toxicity.

The Commission's regulatory definitions that interpret and supplement the statutory definitions provide specific tests that can be used to determine whether a product is acutely toxic by oral ingestion, inhalation, and skin contact. 16 CFR 1500.3(c)(2). However, there currently is no

corresponding regulatory definition to apply to products presenting a risk of chronic toxicity.

The Commission has long taken the position that the statutory definition of toxic includes both acute and chronic toxicity. Several regulations issued under the FHSA have addressed chronic hazards associated with a variety of products, such as lead (a neurotoxin), 16 U.S.C. 1500.17(a)(6), asbestos (a carcinogen), *id.* § 1500.17(a)(7), and vinyl chloride (a carcinogen), *id.* § 1500.17(a)(10). Another example of the Commission's action regarding chronic hazards is its Statement of Interpretation and Enforcement Policy on methylene chloride which notified the public that, due to risk of cancer, the Commission considered household products containing methylene chloride to be hazardous substances subject to FHSA labeling requirements. 52 FR 34698 (1987).

Congress and the courts have also recognized the Commission's authority to regulate chronic hazards under the FHSA. In *Gulf South Insulation* v. *CPSC*, 701 F.2d 1137, 1148–50 (5th Cir. 1983), the Fifth Circuit ruled that the FHSA would be the proper statute under which the Commission could ban urea-formaldehyde foam insulation if the Commission could establish a proper evidentiary basis for concluding that the product presented a cancer risk (a chronic hazard). Also, Congress indicated its expectation that the Commission would address chronic hazards through the FHSA. 15 U.S.C. 2080(b)(1)(C) and (2)(A)(iii) (CHAP to review data before Commission can ban a product that contains a carcinogen, teratogen, or mutagen).

B. The Supplemental Definition

The supplemental regulatory definition finalized today amends the regulatory definition of "toxic" to provide a definition that will include chronic toxicity, not just acute. The Commission hopes that this will clarify the definition and fill the gap in the Commission's current regulatory definition of "toxic."

The Commission is issuing the supplemental definition under the authority of section 10 of the FHSA which authorizes the Commission to issue regulations "for the efficient enforcement of this Act." Having this definition will improve the Commission's enforcement capabilities since the staff would not have to prove the meaning of chronic toxicity in each enforcement action. The Commission also believes that the definition will be helpful to manufacturers since it will clarify that chronically toxic substances are "toxic" (and must be labeled appropriately) under the FHSA. The supplemental definition discusses the particular chronic hazards of cancer, neurotoxicity, and developmental or reproductive toxicity. However, the definition is not limited to these hazards, but includes other chronic hazards.

The Commission has simplified the proposed definition. Some commenters felt that the proposed definition would eliminate the flexibility necessary to properly consider all factors affecting risk. They objected to an automatic risk level and automatic safety factors.

The Commission's intention in issuing the proposed guidelines and definition was to provide a balance of flexibility and certainty. The Commission did not intend to impose an automatic system that leaves no room for expert judgment. The general principle that determination of chronic hazards is a complex matter requiring the assessment of many factors is stated throughout the proposed and final guidelines.

After reviewing the comments and considering how the proposed definition would be implemented, the Commission decided to issue a broad definition rather than the more rigid one proposed. The final definition will clearly inform the public that chronic hazards are covered under the FHSA. It will also allow the flexibility intended by the Commission. This does not mean, however, that manufacturers will lack direction on when to label products that may present chronic hazards. The guidelines present exhaustive discussions of the chronic hazards of cancer, neurotoxicity, and reproductive and developmental toxicity, as well as the principles of exposure and risk assessment. The guidelines clearly recommend a risk level of 1×10^{-6} for carcinogens and certain safety factors for neurotoxins and reproductive and developmental toxicants. The guidelines provide that these levels should generally be followed in making labeling decisions, but they recognize that sound scientific data may warrant deviation from these levels.

Rather than requiring set risk levels, the final supplemental definition defines "toxic" as including such chronic toxicants as carcinogens, neurotoxins and reproductive and developmental toxicants.

VIII. Significant Comments and Responses

A. Comments Concerning the Codification

Comment. Several commenters expressed concern that art materials intended for adults and for use outside of the household are not covered by the Commission's interpretation of LHAMA.

Response. As explained more fully in section III.D of the preamble, the Commission construes this exclusion to be very narrow. LHAMA mandated ASTM D–4236 as a Commission rule under section 3(b) of the FHSA. Section 3(b) applies to substances intended or packaged in a form suitable for use in a household or by children. Thus, a substance that is not so packaged or intended is not covered by a section 3(b) rule. However, the Commission believes that it will be a very rare art material whose use is not anticipated in the household or by children.

This is particularly true since many artists do not separate their households from the area where they use art materials.

Comment. Some commenters stated that the final rule should clearly require a conformance statement on all art material products.

Response. As explained in section III.B. of the preamble, the Commission understands ASTM D–4236 to require that art material products that do not require chronic hazard labeling provide a conformance statement indicating that they conform to the requirements of ASTM D–4236.

Comment. A few commenters observed that the Commission needs to be able to amend ASTM D–4236 if ASTM changes any provisions of the standard.

Response. LHAMA provided for the Commission to amend the standard once it has provided an opportunity for written comments. If the change is not one initiated by ASTM, oral comments must also be permitted. The procedure for amending the standard is discussed in section III.F. of the preamble.

Comment. Several commenters noted the difficulty in defining "reasonably foreseeable or customary use" of an art material. This problem was also noted for other materials.

Response. The Commission agrees that this concept is difficult to define and may be particularly so with art materials. As the discussion in section IV.C. of the preamble indicates, the Commission has generally given a broad interpretation to the term.

Comment. Several commenters questioned the need for boardcertified toxicologists to review the formulations of art materials, and some recommended deleting this requirement from ASTM D–4236.

Response. As explained in section III.E. of the preamble, ASTM D–4236 defines the term "toxicologist" for

purposes of that standard as a board certified toxicologist or physician. The Commission can only change this requirement by the rulemaking process that LHAMA provided to amend the standard. The process for amending the standard is discussed in section III.F. of the preamble.

However, the staff does not believe that, in most instances, whether a toxicologist is board certified or not will be crucial to the analysis performed. Rather, the Commission is primarily concerned that the review is conducted by a person who has sufficient knowledge based on education, training, and experience and that the review is based on appropriate criteria. Section III.E. of the preamble explains that as a matter of enforcement policy, the Commission will not require that all art material reviews be conducted by a board certified toxicologist.

Comment. One commenter stated that no scientific and epidemiological data exist to suggest that consumers are being harmed by current use of art materials.

Response. The Commission is not asserting that any particular art material does or does not present a hazard. The guidelines set up a process to determine whether a product presents a chronic hazard. Congress has made the judgment that there is a need for a standard relating to the chronic health risk of art materials and that the Commission should develop guidelines.

Comment. Some individuals and organizations have sought clarification of the term "art material," and they have asked for some guidance on how the Commission will interpret the term as defined in LHAMA.

Response. Congress provided a broad definition of the term "art material." With the exception of certain products regulated under other statutes, the term is defined as "any substance marketed or represented by the producer or repackager as suitable for use in any phase of the creation of any work of visual or graphic art of any medium." 15 U.S.C. 1277(b)(1). The Commission has not developed any supplemental definition that would further define this term. However, some guidance on the Commission's interpretation of this term is provided in the discussion earlier in the preamble in section III.D.

B. General Comments Concerning Guidelines

Comment. One commenter suggested that the Commission should issue chemical-by-chemical "guidelines" somewhat like the lists that are developed by the state of California under Proposition 65. Similar comments suggested that the Commission develop substance-specific lists of carcinogens, sensitizers, neurotoxins, and developmental/reproductive toxins.

Response. The Commissions's action fulfills the Congressional intent behind LHAMA and is consistent with the FHSA. The Commission believes that its approach strikes a balance between the desire for certainty and the need to allow expert judgment. As explained in the preamble and the guidelines, many factors must be considered and assessments made to come to the determination that a substance is a "hazardous substance" under the FHSA. A simple list of substances would not reflect the complexities involved in this determination.

Comment. Commenters expressed views on both sides of the issue of the scope of the guidelines, that is, whether they should apply to products other than art materials. Chemical Manufacturers Association ("CMA"), for one, suggested that the Commission address non-art materials in a separate proceeding.

Response. As stated elsewhere in the preamble, the guidelines are intended to help manufacturers and others in determining whether their product presents a chronic hazard and, therefore, must be labeled under the FHSA. These same considerations are equally appropriate for art materials and for other products subject to the FHSA. The guidelines are not mandatory. Thus, to say that they only "apply" to art materials makes no sense since their use will be equally helpful to the manufacturers of art materials and of other products subject to the FHSA.

Comment. Several commenters suggested that the Commission convene a Chronic Hazard Advisory Panel ("CHAP"). CMA, for example, envisions the CHAP as a "screening mechanism" to identify particular consumer products "that deserve a full evaluation for potential chronic health risks." The CHAP would conduct hazard determinations on materials nominated by CPSC. There would be an opportunity for public comment. If warranted, the CHAP would assess potential exposure and, if there was significant exposure potential, conduct a risk assessment. The CHAP would then make recommendations to CPSC regarding labeling. CSMA recognized that the Commission is not required to consult a CHAP before issuing the guidelines, but suggested this "as a matter of sound administrative practice." Another commenter suggested that the Commission should establish a CHAP to review the need to expand the chronic hazard guidelines to product categories other than art materials

Response. As explained more fully in section V.B. of the preamble, the Commission must establish a CHAP in certain specified situations. The only action under the FHSA that requires the Commission to consult a CHAP is rulemaking to ban a particular substance.

In issuing these guidelines, however, the Commission is not promulgating a binding rule, is not seeking to ban a substance, and is not taking action with respect to any particular substance. The CHAP's purpose is to review particular products and substances. CHAP review is not appropriate in this case. The chronic hazard guidelines do not relate to any particular products or substances, but they provide guidance for determining, in general, whether a product can present a chronic health hazard.

Comment. In a somewhat similar vein, some commenters suggested that the Commission should regulate chronic hazards under the CPSA rather than the FHSA. They thought that the Commission should address specific consumer products and consult CHAPs in the process of doing this.

Response. As discussed in the preamble, the FHSA provides authority for the Commission to regulate chronic hazards. Although the Commission may have the authority to proceed under the CPSA, the FHSA is the more appropriate statute. The FHSA specifically requires the labeling of hazardous substances. The Commission has acted in the past to provide for chronic hazard labeling under the authority of the FHSA (e.g., methylene chloride). In fact, if the Commission were to issue chronic hazard guidelines under the CPSA, it may have to first issue a rule under section 30(d) of the CPSA finding that it is in the public interest to proceed under the CPSA rather than the FHSA.

Comment. CMA commented that the Commission has not given adequate notice to extend the chronic hazard guidelines from art materials to other products covered by the FHSA. CMA stated that the proposed guidelines did not adequately explain the Commission's authority and did not address the economic effects of the extension.

Response. The Commission believes that adequate notice was provided. The proposed guidelines clearly stated that because the scientific principles behind the guidelines are not affected by the types of products under consideration, manufacturers could use the proposed guidelines to aid their determination of whether a product covered by the FHSA presents a chronic hazard. The

commission received 47 written comments, including several on the very issue of the scope of the guidelines, and 15 people presented testimony at the public hearing in October.

Moreover, as explained in the preamble, the chronic hazard guidelines are not mandatory and are not being issued as substantive, binding rules. Rather, they are intended as guidance for manufacturers and others who must determine if their product requires labeling under the FHSA.

The Commission believes that it has adequately addressed the economic effects of the chronic hazard guidelines. The guidelines impose no new requirements on manufacturers. It is the FHSA that requires proper labeling of hazardous substances. The guidelines represent the CPSC's interpretation of the current scientific concensus regarding chronic health hazard assessment. Furthermore, the guidelines do not require any review of non-art materials by a toxicologist. This is a requirement of LHAMA and is directed exclusively at art materials.

Some commenters, including CMA may incorrectly believe that toxicological review would be required of all products subject to the FHSA. The requirements associated with the codification of the ASTM D-4236 apply only to art materials.

Comment. Several commenters stated that the Commission should clarify that chronic hazards covered by the FHSA are those that have the potential for "substantial" injury or illness.

Response. The FHSA definition of "hazardous substance" at issue in these guidelines does concern substances that may cause "substantial personal injury or substantial illness." 15 U.S.C. 1261(f)(1). The Commission's regulatory definitions provide guidance in interpreting this term. The applicable regulation states: "Substantial, personal injury or illness' means any injury or illness of a significant nature. It need not be severe or serious. What is excluded by the word 'substantial' is wholly insignificant or negligible injury or illness." 16 CFR 1500.3(c)(7)(ii).

C. Comments On Scientific Issues of the Guidelines and Definition

1. General

Comment. Commenters noted that it is important to keep the guidelines flexible and that rigid adherence to default factors (i.e., numerical factors to be used in the absence of data for the particular substance or circumstances) should not be required.

Response. The guidelines are intended to be flexible. This is stated very clearly in the guidelines as proposed and finalized. Default assumptions such as those used in exposure and risk assessment are, by definition, to be used in the absence of appropriate data. The guidelines permit the replacement of default assumptions with data-based alternatives. Alternative approaches should be scientifically defensible and supported by appropriate data.

Comment. Some commenters suggested that the guidelines should clarify that lack of significant bioavailability (or exposure) of a substance that would otherwise be a chronic toxicant will result in that substance being exempt from consideration as a "hazardous substance" under the FHSA.

Response. The proposed guidelines explained that for a substance to be a "hazardous substance" under the FHSA it must have the potential to be toxic and present a significant risk of adverse health effect through customary or reasonably foreseeable handling or use. The proposed guidelines also explained that this second factor reflects the person's exposure to the toxic component or the component's bioavailability. 56 FR 15674. The final guidelines reiterate this point.

Comment. Several commenters suggested that CPSC should specify using a species extrapolation method based on body weight since the use of the proposed "surface area correction" is not supported by the science.

Response. The science does not more strongly support one specific choice for a species extrapolation factor over another. Such a factor is commonly used to predict human cancer risks on the basis of results in animals. It is generally agreed that the best choice for such a factor lies within the range of the body weight method cited by the commenters, and the "surface area" method proposed in the guidelines. The FDA has used the body weight method in the past, and CPSC and the EPA have used the "surface area" method.

However, CPSC staff has been working closely with EPA, FDA, OSHA, and other Federal agencies to adopt a unified approach for species extrapolation (a factor related to weight ratio of humans and animals to the three-fourths power, which is in the middle of the range previously described). The guidelines state that this approach should be used when the unified Federal effort is adopted. There is extensive scientific justification and much peer review associated with this process. The Commission does not believe any change to this discussion in the proposed guidelines is warranted.

Comment. A few commenters stated that CPSC proposes to select data which produces the highest risk estimate. They suggested that the CPSC should encourage users to evaluate all appropriate data sets, and that the most scientifically relevant data, preferably human epidemiology, should be regarded as the key data to use for dose-response modeling.

Response. The proposed and final guidelines do not specify using data that produce the highest risk estimate. In choosing which data sets will serve as the basis for risk estimates, toxicologists should review all the data. The guidelines state that expert judgment is to be used in this, as well as in the many other choices which are part of the risk characterization process. For example, a method is presented which combines the results from different sexes, as opposed to only calculating risk from the highest responding sex. Furthermore, statements are made within the guidelines indicating that human epidemiology, when adequate, is the preferred source of data for human risk characterization.

Comment. Several commenters objected that the proposed definition of "toxic" would remove flexibility and require automatic application of a specified risk level for carcinogens and safety factors for other chronic toxicants.

Response. After considering these comments and how the proposed definition would work in practice, the Commission decided to revise the definition so that it defines "toxic" with respect to chronic toxicity but does not specify particular trigger levels. The definition is discussed in section VII of the preamble.

2. Cancer

Comment. Several commenters suggested that the guidelines' consideration of benign tumors as evidence of carcinogenicity should be similar to the approach of the Environmental Protection Agency and the International Agency for Research on Cancer (IARC), which consider such tumors as "limited evidence," and not "sufficient evidence." The grouping of benign and malignant lesions, they assert, is controversial and is only appropriate when certain criteria, like histogenic cell type, are met.

Response. The basis for considering benign tumors as part of "sufficient evidence" under certain conditions, and combining benign tumors with malignant tumors was discussed in the proposed guidelines. The CPSC believes that a benign tumor, if it has the potential to progress to malignancy, or is

life-threatening, should be considered to have the same potential health risk as if it is a malignant tumor. Current information supports combining benign and malignant tumors when scientifically defensible (e.g., same cell type in an organ or tissue). This is one of the principles of the consensus document proposed by Federal government agencies under the aegis of the Office of Space and Technology Policy. As it is rarely found that chemicals cause only benign tumors (in a review of 300 National Toxicology Program bioassays by Huff in 1988), the CPSC staff believes since a benign tumor may be life-threatening itself, or may be transitioning to malignancy, it should be treated as a malignant tumor unless there is adequate evidence showing that these possibilities are unlikely to occur.

Comment. Several commenters observed that increased tumor incidence at independent multiple sites are not necessarily independent observations and should not be treated as such in the guidelines. Tumors resulting from metastasis are not considered as separate tumors. Significance of multiple site tumors should be considered in the same way as that by EPA.

Response. The issue of tumors produced at multiple sites was discussed in the proposed guidelines. The phrase "sites of independent origin" means independent cancers which originate at unique sites and not that the same cancer metastasizes to a different site where cancer is reestablished. Thus, metastasis of a primary tumor to different sites will not be counted as different primary tumors because they would not have independently originated. The staff believes that the ability of a chemical to independently produce tumors at multiple sites indicates that the chemical has a wider range of carcinogenic potential similar to such an indication from responses in multiple strains, species, or experiments. No information was found in the comments to warrant any change in this position.

Comment. Several commenters stated that according to the Commission's proposals, a single study in humans which shows only limited evidence, or a study in animals which shows "sufficient evidence," is all that is required to determine that a substance is toxic under the FHSA due to chronic toxicity. They observed that in general, consistent findings from multiple human studies or multiple species are necessary to ensure valid hazard identification for this type of toxicity.

Response. Evidence from a study or studies taken together must be evaluated by the toxicologist. If a single extremely well conducted, non-biased study shows a powerfully significant effect, it by itself can serve as a basis for "sufficient evidence" of a toxic effect.

Epidemiological studies are very complex, and generally have inherent problems, such as exposure to multiple chemicals and problems ascertaining exposure. Much of this complexity leads to the evidence falling into the "limited evidence" category. CPSC staff believes that an epidemiological study or studies, which provides convincing evidence of a causal relationship between the incidence of cancer (or other chronic effects) and exposure to a chemical, but in which chance, bias, or other confounding factors could not be absolutely ruled out (limited evidence), may warrant the characterization of a chemical as toxic (probable human carcinogenic substance) under the FHSA. The criteria in these guidelines are not intended to be mechanically applied, but rather should be interpreted with the exercise of expert technical judgment. A single animal study with a response at only one dose will not normally lead to a conclusion that the substance is "toxic" under the guidelines.

Comment. Several commenters suggested that a "weight of the evidence" approach used by EPA should be followed in place of a "strength of the evidence" approach used by IARC in categorizing the evidence. CPSC, they observed, seems to have adopted the "strength of the evidence" approach. The commenters suggested that the guidelines should emphatically direct the consideration of all available information, including tests that show negative responses, as part of any evaluation.

Response. Both approaches include evaluation of all the available data regardless of the positive or negative results. CPSC's approach, which is not designated by any name, is similar to that of EPA and IARC; it also includes evaluation of all the available data. CPSC's approach does require a certain amount and quality of positive data before a finding of "toxic" can be made, but CPSC's guidelines also state that certain data and evidence can negate the impact of the positive data. The Commission believes that the approach adopted in the guidelines to evaluate carcinogens is a sound one, because it allows consideration of all the available data and not just the positive data.

3. Neurotoxicity

Comment. Numerous commenters noted that since LHAMA is concerned with only chronic effects, acute neurotoxic effects should not be considered. Discussion in the proposed guidelines on neurotoxicity, they stated, is too broad and would cover everything including water. Consideration should be limited to the agents which primarily affect the nervous system; only direct neurotoxic effects should be included in the definition. Effects due to overdosing, or alterations from baseline should not be considered as an indication of neurotoxicity unless statistical significance can be demonstrated.

Response. The guidelines do address only chronic effects. The nervous system is integrally connected to the functioning of all the other systems in an organism, which complicates the interpretation of neurotoxic effects. Effects can be chronic under several circumstances. These include long-term exposure followed by the effect, short-term exposure followed by an effect occurring at some time in the future, and an immediate effect due to short-term exposure which then lasts for a prolonged period of time. "Acute" in this case would refer to only those immediate effects, from short-term exposure, which are rapidly and completely reversible. The terms "short," "prolonged," and "immediate" are general guides to the interpreting toxicologist, who must decide from the nature of the studies if the effect is acute or chronic.

Comment. Several commenters stated that defining "sufficient evidence" by statistics is not appropriate since some results may be statistically significant due to random variability. They suggested that results must be statistically significant and biologically plausible, that "limited evidence" should also require biological plausiblity, and that the "possible neurotoxic substances" class should be deleted. Neurotoxicity criteria, they commented, are impractical to determine an appropriate hazard warning.

Response. Although it is possible that some neurotoxicity findings may be the result of false positives, this is accounted for by the guidelines. For human studies, the studies must be of high quality, and bias (which could lead to a false positive) must be considered. For animal studies, the effects must be statistically significant in more than one good quality study. Expert technical evaluation includes examination of reliability, sensitivity, and validity along with the requirement that a study should be well designed and conducted. Biological plausibility is a factor that increases confidence in a result, but by no means is it a prerequisite for using

the study as a basis for a finding of toxicity. In addition, it is clearly stated that evidence derived from animal studies that has been shown not to be relevant to humans is not included in the consideration of the neurotoxicity of a substance. The "possible neurotoxic substances" class is important to retain because it could indicate that more work is necessary on a particular chemical, and it gives the basis why the current evidence is not sufficient to conclude that a substance is toxic.

4. Reproductive and Developmental Toxicity

Comment. Some commenters stated that it is inappropriate to list a chemical in the "sufficient" category if it has been found to be active in only one species, regardless of the number of endpoints. A single statistically significant endpoint is not "sufficient" evidence to classify a material as a reproductive or developmental toxicant.

Response. The staff believes a good quality study with significant changes in multiple endpoints using multiple doses, routes of administration, or strains, constitutes a degree of toxicity in animals that is predictive of probable harm to humans and thereby warrants further assessment of exposure, risk, and bioavailability. If an effect occurs more than once (at two dose levels or two sites, for example), or if there are multiple effects, the possibility that the observed reproductive or developmental toxicity is an anomoly is greatly reduced.

Comment. Some commenters stated that maternal toxicity and its relationship to developmental toxicity should be evaluated and integrated into the interpretation of a study. Developmental toxicity, they stated, should not be automatically discounted as secondary when it is associated with maternal toxicity.

Response. The Commission agrees with this comment. The proposed guidelines stated "maternal toxicity * * * must be evaluated and accounted for in the interpretation of a study. The toxic effect(s) observed in a positive study *should* be significant at one or more doses in the absence of maternal toxicity." 56 FR 15684 (emphasis added). The final guidelines have been revised to clarify this point and state that toxicity is not automatically discounted as secondary when associated with maternal toxicity.

5. Bioavailability.

Comment. One commenter observed that CPSC proposes to set the dermal penetration rate for chemicals present in mixtures at 100 percent. CPSC should require skin penetration rates based on the physical-chemical characteristics of an art material, the commenter stated. While direct measurement of the skin penetration is desirable, in numerous instances it is impractical. Alternatively, other indirect approaches must be relied upon to estimate systemic doses from skin contact; and any default value, particularly one as severe and overly simplistic as 100 percent, must be left to rare and extreme circumstances.

Response. The proposed CPSC bioavailability guidelines did not set the dermal penetration rate for chemicals at 100 percent. In fact, the guidelines as proposed and finalized specify the use of indirect approaches, including use of physicochemical data, to estimate dermal bioavailability where appropriate. The proposed guidelines, at section III.F.2.c.i (56 FR 15590) clearly indicated that either a default value may be assumed or a bioavailability assessment may be performed. That paragraph also states that "the default value should be used when there are no adequate data which would lead to an alternative approach." The following paragraph of the proposed guidelines generally describes the alternative approaches and the conditions under which they can be used to estimate bioavailability.

The type of data which may be used in a quantitative bioavailability assessment are discussed in subsection (b) of VI.F.2.c.i. A number of acceptable methods of measuring dermal penetration are also specifically identified in the technical support document for the bioavailability guidelines available through the CPSC's Office of the Secretary. They include *in vivo* bioavailability studies, isolated perfused skin studies, *in vitro* studies using excised skin, physiologically based dermal absorption models, surrogate data such as octanol:vehicle partition coefficients and bioavailability data from surrogate compounds. It is stressed throughout the guidelines that all factors expected to affect dermal penetration must be considered in the assessment. This is especially important when bioavailability is based on *in vitro*, surrogate compound, or physicochemical data.

Comment. One commenter states that in the proposed guidelines, CPSC fails to acknowledge the range of information that may be relied upon to make estimates of systemic doses from skin contact with chemicals reliably in the absence of direct empirical measurements. The information lacking from CPSC's proposed guidelines, the commenter states, includes viscosity of a chemical mixture, the molecular weight of each substance, the polarity of each substance in a mixture, and the lipophilicity of each compound.

Response. This comment is incorrect. Section III.F.2.c.ii(c) of the proposed guidelines (56 FR 15594) acknowledged a large number of factors that impact dermal bioavailability including three of the four examples cited in this comment. Lipophilicity, molecular size, and degree of polarity are all discussed in the second paragraph of the section as important chemical-specific determinations of dermal absorption.

This section of the guidelines describes several vehicle-specific determinants of dermal absorption but does not include viscosity. The commenter claims that "high viscosity acts as a barrier to absorption through the skin" based on "many incidental observations" related to pen and marker inks. The staff is unaware of scientific data that show viscosity retards skin penetration, although it is generally recognized that viscosity will affect dermal migration (migration of a substance from a product to the skin surface). Dermal migration is discussed in the guidelines for assessing exposure (VI.F.1.c.iii). Finally, the fourth paragraph of the skin permeability section describes the major physiological and other factors expected to influence dermal absorption. Hydration of the stratum corneum and volatility of the mixture, also mentioned elsewhere by the commenter, are discussed in that section.

Comment. One commenter asked how a hazard can be established and estimated when the exposure is infinitesimally smaller than doses known to produce any effects in animals. The commenter stated that hazards are estimated by direct exposure to a substance regardless of the route of exposure, and, more often than not in art materials, the particular ingredients of concern are not readily bioavailable.

Response. This comment is interpreted to question the basis on which CPSC can ever consider ingredients contained in art materials as hazardous when: (a) Users are exposed to much smaller amounts of these substances than cause adverse effects in experimental animals, and (b) the routes of human exposure to art materials are often such that the ingredients would not be readily bioavailable.

The first part of the question was addressed in section III.F.4.b of the proposed guidelines on acceptable daily intake. The ADI is the maximum daily dose of a chronically toxic substance (as determined by other sections of the

guidelines) to which a person can be exposed without presenting an unacceptable risk of injury and illness. The ADI will usually be considerably less than the dose observed to cause an adverse health effect in animals as discussed in subsection (i) and (ii) of this discussion in the guidelines. This is because the observed adverse effect levels in animals, in most instances, have to be adjusted (1) to assure that the toxicity observed at the high levels is acceptably reduced or eliminated at the human exposure levels, (2) to protect for the possibility that humans may be more sensitive to the toxic effect at equivalent administered doses, and (3) to account for the larger expected variation within the human population. Unfortunately, scientific data on which to determine the magnitude of these adjustments are rarely available, necessitating the use of assumptions based on longstanding policies within the regulatory community. However, the guidelines indicate that these assumptions should be replaced with biologically-based approaches when there is valid and convincing scientific evidence that an alternative is clearly superior.

The second part of the comment is addressed within the guidelines for assessing bioavailability. That section of the guidelines describes the situations in which there is a need to assess bioavailability, including when it is anticipated that the routes of human exposure to a toxic substance will differ from those used in an animal toxicity study.

If it is true that exposure to ingredients within art materials are "infinitely smaller" than the doses that produce chronic toxicity in animals and that the ingredients of concern are not bioavailable, then of course there is no hazard. However, this needs to be established through the hazard assessment process.

6. Exposure Assessment.

Comment. One commenter suggested that exposure assessment should be done in accordance with handling instructions on the product package, such as, "use with adequate ventilation."

Response. ASTM D–4236 states that reasonably foreseeable misuse should be considered in assessing risk. Use with inadequate ventilation, for example, is likely to be reasonably foreseeable. Commission regulations also state that under the FHSA "reasonably foreseeable handling or use" includes foreseeable accidental handling or use. 16 CFR 1500.3(c)(7)(iv). Thus, in the context of LHAMA and the FHSA, exposure assessment should not be limited to the manufacturer's instructions.

Comment. Two commenters suggested that CPSC eliminate consideration of incremental exposures when judging the need to label an art material, as suggested in the guidelines for assessing exposure. This provision, they stated, is impractical and unnecessary, and CPSC fails to provide adequate guidance for its implementation. They stated that it will create confusion among users if a product is labeled due to incremental exposures from other sources.

Response. It is often impractical to consider exposures from other sources, although it is sometimes desirable to do so. One example is products containing lead since there is an existing background level near the point where an effect can occur. However, in the context of LHAMA and the FHSA, the focus is clearly on individual products. The proposed guidelines stated in the discussion only that "it may be useful" to define what portion the product-specific exposure is of the total environmental exposure, but the discussion acknowledged the difficulties. The final guidelines clarify that assessment of exposures from other sources is not required, but should generally be noted. Whether other sources should be considered must be determined on a case-by-case basis.

7. Risk Assessment.

Comment. Several commenters objected to CPSC's proposal in the chronic hazard guidelines that an additional ten-fold safety factor be applied to products intended for use by children for all chronic endpoints when calculating the acceptable daily intake, to account for the possibility that children may be more sensitive than adults. Several stated that this was not supported by the scientific data. Some commenters stated that this additional ten-fold factor would have an adverse economic impact on the art materials industry, especially on manufacturers of unleaded glazes used for ceramics. As a result of this safety factor, they stated, 92 product lines which currently do not require warning labels under the Art and Craft Materials Institute's review program will be required to carry warning labels.

Response. As discussed in section IV.E. of the preamble, the Commission has decided not to include additional safety factors for children's products in the final guidelines and definition.

Although children may be more susceptible to many substances than adults, it may be difficult to differentiate between products for children and those for adults, particularly in the area of art materials. This could result in a more widespread use of the ten-fold safety factor than the Commission had intended.

Even if CPSC's proposed ten-fold safety factor were implemented, however, it is questionable whether the extra safety factor for children would actually affect the labeling status of unleaded glazes. According to Dr. Stopford (ACMI's consulting toxicologist), ACMI applies safety factors of its own to risk assessments involving children. In many cases, the ACMI safety factors, which are not required in the proposed guidelines, may be equivalent to or greater than CPSC's proposed ten-fold safety factor. In effect, ACMI's toxicologist has applied redundant safety factors and, as a result, has overestimated risk.

Multiple overestimations of exposure, in total greater than a factor of ten, have been incorporated by ACMI's analysis; these would not be used if CPSC staff were to do the analysis. Of course, ACMI's overestimation of exposure is intentional. It is its means of providing an additional safety factor for children.

In addition, for assessing cancer risk, according to Dr. Stopford, ACMI assumes that children are exposed for 70 years. In comparison, the Directorate for Health Sciences would assume that a child is exposed to a children's product only during childhood. If childhood is considered to last for ten years, then ACMI in effect is applying a seven-fold safety factor of its own which is not directed by CPSC's guidelines. Taken together, ACMI's self-imposed seven-fold safety factor and the 1×10^{-7} acceptable risk directed by the CPSC guidelines, are equivalent to a 70-fold safety factor, while the proposed guidelines required only a ten-fold factor.

Comment. Several commenters stated that the Commission's guidelines and rules should be consistent with those of other agencies, such as OSHA, EPA, and FDA.

Response. Congress mandated the voluntary standard as a Commission standard. The Commission cannot change these provisions without going through the amendment procedures specified in LHAMA. The CPSC's chronic hazard assessment guidelines are almost entirely consistent with the guidelines and methodologies of other agencies, including those mentioned by the commenters. Some of the differences relate to what is required by Congress; for example, LHAMA requires CPSC to address the determination of acceptable daily intake for chronic hazards.

The few technical differences between CPSC and other agencies have been carefully considered by CPSC. For example, two major differences between CPSC's guidelines and EPA's guidelines are the use of benign tumors and the treatment of tumor responses at multiple sites. EPA, which is in the process of revising its cancer guidelines, is reconsidering its position on these two points. It is quite possible that EPA's revised guidelines will be in agreement with CPSC's on these points.

CPSC is working with other agencies to harmonize risk assessment methodologies. For example, CPSC staff has been working with EPA, FDA, and OSHA to adopt a uniform approach for species-to-species extrapolation. CPSC's proposed guidelines state clearly that the uniform approach (body weight ratio to the three-fourths power) will be used when the proposal is finally adopted.

Under the Hazard Communication Act, OSHA may require manufacturers to warn workers if there is a single, well designed study showing a statistically significant effect for a health hazard such as cancer. The toxic potency and exposure are not necessarily considered, as they are under LHAMA and the FHSA. Therefore, it is possible that a product could require a warning in the workplace, but not require a label when sold as a consumer product. Occupational exposures are typically greater than consumer exposures from similar materials.

Regarding labels themselves, the Commission is not requiring any labeling beyond what is required by LHAMA and FHSA. The staff is revising its 1979 labeling guide so that it will provide guidance on developing chronic hazard labeling.

D. Comments Concerning Labeling

Comment. CMA suggests that the Commission adopt the ANSI standard for Hazardous Industrial Chemicals (Z129.1–1988) for precautionary labeling of chronic hazards.

Response. The Commission is not prescribing particular labeling requirements. Some requirements for art materials are mandated by LHAMA. Other materials must adhere to the requirements of section 2(p) (1) of the FHSA and regulations previously issued under that authority (e.g. for prominence, placement, and conspicuousness at 16 CFR 1500.121). The staff will, in the future, develop some general guidance about the design and content of labels warning of chronic hazards.

Comment. Several commenters noted that while the proposed guidelines and supplemental definition of toxic would apply to all products subject to the FHSA, not just art materials, the Commission did not include additional labeling requirements for what the chronic hazard labels should say except in the case of art materials.

Response. Neither the guidelines nor the definition specify labeling requirements beyond those already in force under the FHSA. ASTM D–4236, now codified as a Commission standard for art materials, does provide some examples of labels that may be appropriate to warn of chronic hazards. These warnings may also be appropriate for other products subject to the FHSA that present a chronic hazard. However, the suggested labeling may not be sufficient to satisfy all the requirements of section 2(p)(1) of the FHSA for art materials or other household products, especially mixtures containing various chemicals. It is the manufacturer's responsibility to determine the product's characteristics and to design appropriate labeling. The staff is in the process of revising its 1979 labeling guide for products that present an acute hazard. The updated version will provide guidance on developing warning statements for products that pose a chronic hazard.

Comment. One commenter suggested that since it is not known how various components of art materials interact, the most informative labeling might be to state "Contains (name of toxic substance). Use this product with caution and as intended or instructed."

Response. Art material mixtures may be more or less hazardous than the components themselves because of synergistic or antagonistic reactions. For this reason, labeling may not reflect the true effect of the mixture if it is based on the extent to which one component is a carcinogen, neurotoxicant, or reproductive or developmental toxicant. Moreover, as explained in the guidelines, bioavailability and exposure must be considered. Labeling of art materials should be accurate and as specific as possible in terms of precautionary statements and consequences of ignoring the warning. Specificity increases the likelihood that users would take precautionary measures and reduces the likelihood that the product will be used in a manner perceived as safe, but which may not include the appropriate safety measures. Thus, mixtures should be evaluated based on existing scientific data so that the label can reflect the true nature of the hazard.

E. Comments Concerning Economic Impact

Comment. Some commenters expressed concern about the burden that would be placed on each manufacturer having products assessed by toxicologists and submitting to the Commission assessments of the potential chronic hazard of each product. Additionally, if a product were mistakenly required to have chronic hazard labeling under the guidelines, this would be tantamount to banning the product, since no consumer would buy the product. Thus, the guidelines should be carefully thought through. CMA suggested that the Commission issue a separate notice of proposed rulemaking to address such economic concerns.

Response. The preamble attempts to clarify that the requirement that a manufacturer provide a toxicologist with formulations of the manufacturer's products and that the manufacturer submit to the Commission the criteria used to determine chronic toxicity only applies to art materials. As discussed in the preamble, with products other than art materials, it is the manufacturer's responsibility to see that products are properly labeled, but the means used to reach this goal are left to the manufacturer. The guidelines impose no labeling requirements beyond those already in existence in the FHSA.

Even with art materials, however, LHAMA and ASTM D–4236 do not require a risk assessment of each product be submitted to the Commission. Rather, the producer or repackager of an art material must provide the Commission with a summary of the criteria a reviewing toxicologist uses to determine chronic toxicity and a list of those specific products that require chronic hazard labeling.

Manufacturers who have credible reasons to believe that their products are safe or else are applying the appropriate warning labels, would not need to reevaluate their products against the guidelines. The guidelines and supplemental definition, in and of themselves, do not increase the regulatory burden on manufacturers. The labeling of hazardous substances is mandated by the FHSA, not by the guidelines. The choice of means used for evaluating the hazardousness of a product is left to the manufacturer. However, because failure to properly label a hazardous substance is a violation of the FHSA, and because unnecessary labeling of non-hazardous products may put the firm at a competitive disadvantage, it is in the

firm's interest to have a "carefully thought through" method for evaluating its products. The guidelines and definition should aid the manufacturer in the determination that a product must be labeled under the FHSA. As the preamble and other responses to comments explain, the Commission has given a great deal of thought to the guidelines and definition. The Commission believes that it has adequately addressed the economic concerns expressed and that a separate rulemaking is unnecessary.

Comment. Two commenters requested that the Commission extend the effective date of the final guidelines and definition to six months or one year rather than the 90 days proposed. They stated that additional time is necessary for manufacturers to ensure labeling compliance without excessive hardship.

Response. Neither of the commenters requesting an extension of the effective date are producers of art materials. Thus, only the guidelines and supplemental definition of toxic would apply to these commenters. The guidelines and definition do not impose new requirements on manufacturers of consumer products subject to the FHSA. Therefore, manufacturers of consumer products will not incur additional costs solely because of the adoption of the final guidelines and definition. It is possible that in reviewing the guidelines and definition, a firm may realize that its interpretation of the FHSA requirements has been in error and will incur costs correcting its mistake. However, these costs would be incurred whenever and for whatever reason a firm discovered that it was not in compliance with the FHSA. Furthermore, one of the above commenters stated that it has already "conducted extensive testing to ensure the safety of [its] products and has not discovered any chronic hazard concerns." If responsible evaluation has occurred, the firm is likely to be in compliance with the FHSA. The Commission does not believe that there is any economic justification to extend the effective date.

F. Comments Concerning all Actions

Comment. Several comments raised the issue of preemption. Some commenters stated that the proposed rules might lend strength to an argument that they would preempt state laws dealing with toxic chemicals, and these commenters requested the Commission to state that the rulemaking would not preempt state law. Other comments requested the Commission to indicate that its actions would preempt state law.

Response. The issue of preemption is quite complex and cannot be resolved simply by stating that all contrary state laws are or are not preempted. As the preamble explains more fully, under section 18 of the FHSA, a cautionary labeling requirement under section 2(p) or 3(b) of the FHSA designed to protect against a risk of injury or illness associated with a hazardous substance would preempt non-identical state or local cautionary labeling requirements applicable to that hazardous substance and designed to protect against the same risk of injury or illness. LHAMA mandated ASTM D-4236 as a Commission rule under section 3(b) of the FHSA. As a labeling requirement under section 3(b) of the FHSA, it has preemptive effect in the circumstances stated in section 18(b)(1)(A).

The final chronic hazard guidelines, however, are not mandatory and do not themselves impose any cautionary labeling — requirements. The requirement to place hazard labeling on a substance that is a "hazardous substance" comes from sections 2(p) and 3(b) of the FHSA. The guidelines, in contrast, are an aid to manufacturers and producers in determining whether a product is a hazardous substance. Thus, the guidelines themselves would not directly preempt any non-identical state guidelines.

The supplemental regulatory definition of "toxic" is not itself a cautionary labeling requirement. However, it does work with the labeling requirements under section 2(p) and 3(b). The regulatory definition in itself does not have direct preemptive effect, but the labeling requirements under sections 2(p) and 3(b) would preempt state and local labeling requirements that applied to hazardous substances (as defined in the FHSA and its regulations) covered by section 2(p) or 3(b) and designed to protect against the same risk.

Comment. An ancillary comment was made that the labeling requirements under the FHSA are too weak and vague to preempt state laws.

Response. The requirements of the FHSA are not vague. The FHSA defines the term "misbranded hazardous substance" at section 2(p)(1)(E) as a hazardous substance that "fails to bear a label (I) which states *conspicuously* * * * an affirmative statement of the principal hazard or hazards, * * * or similar wording *descriptive* of the hazard" (emphasis added). This means the labeling must communicate to the consumer an understanding of the potential principal hazard or hazards presented by the product in order to avoid being misbranded and subject to legal action.

In some cases simply restating the defined hazard, such as "FLAMMABLE" will provide a meaningful statement of hazard. In other cases, more descriptive language is necessary, such as for corrosive hazards, statements like "CAUSES BURNS" or "CAUSES SEVERE BURNS" are required to satisfy the FHSA.

The cautionary labeling required under the FHSA must present a balanced perspective of the potential hazards of the product. Many products which may cause chronic health effects may also be acutely toxic and present physical hazards, such as flammability. The suggested labeling for methylene chloride paint strippers had to take into consideration the product's acute inhalation toxicity in addition to the carcinogencity hazard. Therefore, the suggested front panel label statement is "VAPOR HARMFUL" with the instruction "Read Other Cautions and HEALTH HAZARD INFORMATION on back panel" and the back panel statement is "Contains methylene chloride, which has been shown to cause cancer in certain laboratory animals." For products where the only hazard is carcinogenicity and the evidence of increased risk of cancer to humans is clear, the labeling would be more straight forward. In its policy statement regarding the labeling of asbestos containing consumer products, 51 FR 33911, September 24, 1986, the following signal word and statement of hazard were suggested as adequate for asbestos cement sheet products, "WARNING: BREATHING FIBERS MAY CAUSE CANCER" with the hazardous component declared as "Contains asbestos which is known to cause cancer in humans."

Comment. The Chemical Manufacturers Association ["CMA"] commented that the Commission should provide explicit protection for trade secrets.

Response. Again, there is confusion over requirements of ASTM D-4236 for art materials and requirements for other products. The requirement to submit formulation data to a toxicologist and the determining criteria to the Commission applies only to art materials. Thus, the protection of trade secret information is not as wide-spread a problem as some may have believed. A provision of ASTM D-4236, now codified at 16 CFR 1500.14 (b)(8)(i)((C)(2), states that only the reviewing toxicologist shall have access to the product formulation submitted for review. There is an exception if written

permission is given or if the data are provided on a confidential basis to a physician for purposes of diagnosis or treatment.

Section 2(p)(1) of the FHSA requires that the name of the hazardous substance be listed on the label. This is a statutory requirement and is not something the Commission can change. Listing the generic name is acceptable. There is no requirement to spell out the product formulation or the amount of the hazardous substance.

As for submission of data to the Commission, in general, the Commission does provide for protection of trade secret or proprietary information submitted to it if the material is so marked (16 CFR 1015.18). These provisions would apply to the information submitted by art material producers or repackagers under LHAMA, as well as others subject to the FHSA.

IX. Effective Dates

In order to allow sufficient time for manufacturers and packagers to evaluate the guidelines and supplemental definition, the guidelines and definition will take effect 90 days after publication. The final guidelines and definition will apply to products initially introduced into commerce on or after the effective date. The codification of ASTM D-4236 [§ 1500.14(b)(8)] will be effective upon publication.

X. Environmental Considerations

These actions are unlikely to have any effect on the quantity or physical characteristics of, or other changes in, product, materials, or packaging that could impact the environment beyond normal formulation, packaging, or promotional changes currently common among these producers of art materials and other products subject to the FHSA. Therefore, the Commission concludes that the guidelines, definition, and codification will have little or no potential for affecting the human environment and that neither an environmental assessment nor an environmental impact statement is required. See 16 CFR part 1021.

XI. Regulatory Flexibility Act Certification

The Commission is finalizing guidelines which will provide guidance for determining when a product presents a chronic hazard based on animal or human data. The supplemental definition of "toxic" reflects these guidelines and clarifies the meaning of chronic toxicity. The Commission is also codifying the provisions of ASTM D-4236 which Congress mandated as a Commission standard.

The Commission certifies that the guidelines, definition, and codification will not have a significant economic effect on a substantial number of small entities, and therefore no regulatory flexibility analysis need be prepared

List of Subjects in 16 CFR Part 1500

Arts and crafts, Consumer protection, Hazardous materials, Hazardous substances, Imports, Infants and children, Labeling, Law enforcement, Toys.

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

PART 1500—[AMENDED]

1. The authority citation for part 1500 is revised to read as follows

Authority: 15 USC 1261–1277

2. A new § 1500.135 is added to read as follows:

§ 1500.135 Summary of guidelines for determining chronic toxicity.

A substance may be toxic due to a risk of a chronic hazard. [A regulatory definition of "toxic" that pertains to chronic toxicity may be found at 16 CFR 1500.3(c) (2).] The following discussions are intended to help clarify the complex issues involved in assessing risk from substances that may potentially cause chronic hazards and, where possible, to describe conditions under which substances should be considered toxic due to a risk of the specified chronic hazards. The guidelines are not intended to be a static classification system, but should be considered along with available data and with expert judgment. They are not mandatory. Rather, the guidelines are intended as an aid to manufacturers in determining whether a product subject to the FHSA presents a chronic hazard. All default assumptions contained in the guidelines on hazard and risk determination are subject to replacement when alternatives which are supported by appropriate data become available. The following are brief summaries of more extensive discussions contained in the guidelines. Thus, the guidelines should be consulted in conjunction with these summaries. Copies of the guidelines may be obtained from the Office of Compliance and Enforcement, Consumer Product Safety Commission, Washington, DC 20207. [In addition to the chronic hazards discussed below, issues relating to the chronic hazard of sensitization are discussed in 16 CFR 1500.3(c) (5).]

(a) *Carcinogenicity.* Substances are toxic by reason of their potential carcinogenicity in humans when they are known or probable human carcinogenic substances as defined below. Substances that are possible human carcinogenic substances or for which there is no evidence of carcinogenic effect under the following categories lack sufficient evidence to be considered toxic by virtue of their potential carcinogenicity.

(1) *Known Human carcinogenic Substances ("sufficient evidence" in humans).* Substances are toxic by reason of their carcinogenicity when they meet the "sufficient evidence" criteria of carcinogenicity from studies in humans, which require that a causal relationship between exposure to an agent and cancer be established. This category is similar to the Environmental Protection Agency's (EPA) Group A, the International Agency for Research on Cancer's (IARC) Group 1, or the American National Standards Institute's (ANSI) Category 1. A causal relationship is established if one or more epidemiological investigations that meet the following criteria show an association between cancer and exposure to the agent.

(i) No identified bias that can account for the observed association has been found on evaluation of the evidence.

(ii) All possible confounding factors which could account for the observed association can be ruled out with reasonable confidence.

(iii) Based on statistical analysis, the association has been shown unlikely to be due to chance.

(2) *Probable Human Carcinogenic Substances.* Substances are also toxic by reason of their probable carcinogenicity when they meet the "limited evidence" criteria of carcinogenicity in humans or the "sufficient evidence" criteria of carcinogenicity in animals described below. This category is similar to EPA's Group B, IARC's Group 2, or ANSI's Categories 2 and 3. Evidence derived from animal studies that has been shown not to be relevant to humans is not included. For example, such evidence would result when there was an identified mechanism of action for a chemical that causes cancer in animals that has been shown not to apply to the human situation. It is reasonable, for practical purposes, to regard an agent for which there is "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans.

(i) *"Limited evidence" of carcinogenicity in humans.* The evidence is considered limited for establishing a causal relationship between exposure to the agent and cancer when a causal interpretation is

credible, but chance, bias, or other confounding factors could not be ruled out with reasonable confidence.

(ii) *"Sufficient evidence" of carcinogenicity in animals.* Sufficient evidence of carcinogenicity requires that the substance has been tested in well-designed and -conducted studies (*e.g.*, as conducted by National Toxicology Program (NTP), or consistent with the Office of Science Technology Assessment and Policy (OSTP) guidelines) and has been found to elicit a statistically significant ($p < 0.05$) exposure-related increase in the incidence of malignant tumors, combined malignant and benign tumors, or benign tumors if there is an indication of the ability of such benign tumors to progress to malignancy:

(A) in one or both sexes of multiple species, strains, or sites of independent origin; or experiments using different routes of administration or dose levels; or

(B) to an unusual degree in a single experiment (one species/strain/sex) with regard to unusual tumor type, unusual tumor site, or early age at onset of the tumor.

The presence of positive effects in short-term tests, dose-response effects data, or structure-activity relationship are considered additional evidence.

(3) *Possible Human Carcinogenic Substance ("limited evidence" animal carcinogen).* In the absence of "sufficient" or "limited" human data, agents with "limited" evidence of carcinogenicity from animal studies fall into this category. Such substances, and those that do not fall into any other group, are not considered "toxic." This does not imply that the substances are or are not carcinogens, only that the evidence is too uncertain to provide for a determination. This category is similar to EPA's Group C, IARC's Group 3, or ANSI's category 4.

(b) *Neurotoxicity.* Substances are toxic by reason of their potential neurotoxicity in humans when they meet the "sufficient evidence" or "limited evidence" criteria of neurotoxicity in humans, or when they meet the "sufficient evidence" criteria of neurotoxicity in animals.

(1) *Known Neurotoxic Substances ("sufficient evidence in humans").* Substances are toxic by reason of their neurotoxicity and are considered "known neurotoxic substances" when they meet the "sufficient evidence" criteria of neurotoxicity derived from studies in humans which require that a causal association between exposure to an agent and neurotoxicity be established with a reasonable degree of certainty. Substances in this category meet the definition of "neurotoxic" as stated above. "Sufficient evidence," derived from human studies, for a causal association between exposure to a chemical and neurotoxicity is considered to exist if the studies meet the following criteria.

(i) A consistent pattern of neurological dysfunction is observed.

(ii) The adverse effects/lesions account for the neurobehavioral dysfunction with reasonable certainty.

(iii) All identifiable bias and confounding factors are reasonably discounted after consideration.

(iv) The association has been shown unlikely to be due to chance, based on statistical analysis.

(2) *Probable Neurotoxic Substances.* Substances are also toxic by reason of their probable neurotoxicity when they meet the "limited evidence" criteria of neurotoxicity in humans, or the "sufficient evidence" criteria derived from animal studies. Evidence derived from animal studies that has been shown not to be relevant to humans is not included. Such evidence would result, for example, when there was an identified mechanism of action for a chemical that causes neurotoxicity in animals that has been shown not to apply to the human situation.

(i) *"Limited evidence" of neurotoxicity in humans.* The evidence derived from human studies is considered limited for neurotoxicity when the evidence is less than convincing, *i.e.*, one of the criteria of "sufficient evidence" of neurotoxicity for establishing a causal association between exposure to the agent and neurotoxicity is not met, leaving some uncertainties in establishing a causal association.

(ii) *"Sufficient evidence" of neurotoxicity in animals.* Sufficient evidence of neurotoxicity derived from animal studies for a causal association between exposure to a chemical and neurotoxicity requires that:

(A) The substance has been tested in well-designed and -conducted studies (*e.g.*, NTP's neurobehavioral battery, or conforming to EPA's neurotoxicity test guidelines); and

(B) The substance has been found to elicit a statistically significant ($p < 0.05$) increase in any neurotoxic effect in one or both sexes of multiple species, strains, or experiments using different routes of administration and dose levels.

(3) *Possible Neurotoxic Substances.* "Possible neurotoxic substances" are the substances which meet the "limited evidence" criteria of neurotoxicity evidence derived from animal studies in the absence of human data, or in the presence of inadequate human data, or data which do not fall into any other group. Substances in this category are not considered "toxic."

(c) *Developmental and Reproductive Toxicity.—(1) Definitions of "Sufficient" and "Limited" Evidence.* The following definitions apply to all categories stated below.

(i) "Sufficient evidence" from human studies for a causal association between human exposure and the subsequent occurrence of developmental or reproductive toxicity is considered to exist if the studies meet the following criteria:

(A) No identified bias that can account for the observed association has been found on evaluation of the evidence.

(B) All possible confounding factors which could account for the observed association can be ruled out with reasonable confidence.

(C) Based on statistical analysis, the association has been shown unlikely to be due to chance.

(ii) "Limited evidence" from human studies exists when the human epidemiology meets all but one of the criteria for "sufficient evidence"; *i.e.*, the statistical evidence is borderline as opposed to clear-cut, there is a source of bias, or there are confounding factors that have not been and cannot be accounted for.

(iii) "Sufficient evidence" from animal studies exists when

(A) Obtained from a good quality animal study; and

(B) The substance has been found to elicit a statistically significant ($p < 0.05$) treatment-related increase in multiple endpoints in a single species/strain, or in the incidence of a single endpoint at multiple dose levels or with multiple routes of administration in a single species/strain, or increase in the incidence of a single endpoint in multiple species/strains/ experiments.

(iv) "Limited evidence" from animal studies exists when:

(A) Obtained from a good quality study and there is a statistically significant ($p < 0.05$) treatment-related increase in the incidence of a single endpoint in a single species/strain/ experiment at a single dose level administered through only one route and such evidence otherwise does not meet the criteria for "sufficient evidence"; or

(B) The evidence is derived from studies which can be interpreted to show positive effects but have some qualitative or quantitative limitations with respect to experimental procedures (*e.g.*, doses, exposure, follow-up, number of animals/group, reporting of the data,

etc.) which would prevent classification of the evidence in the group of "sufficient evidence."

(2) *Developmental Toxicants.* Substances are toxic by reason of their potential developmental or reproductive toxicity when they meet the "sufficient evidence" or "limited evidence" criteria of developmental or reproductive toxicity in humans, or when they meet the "sufficient evidence" criteria of developmental or reproductive toxicity in animals. The Food and Drug Administration (FDA) and the European Economic Community (EEC) have developed categories for teratogens but not other developmental toxicants. The teratogen guidelines limit the information only to structural birth defects and do not include other hazards of developmental toxicity such as embryonal death, fetal death, or functional deficiencies which are also important in assessing the overall toxicity of a substance when administered during pregnancy. Recently, EPA has proposed a system for classifying developmental toxicity. The Occupational Safety and Health Administration (OSHA) has not yet developed any classification for developmental toxicity. The commission has established the following categories for determination of developmental toxicity according to the available evidence.

(i) *Known Human Developmental Toxicant ("sufficient evidence in humans").* A substance is considered a "known human developmental toxicant" if there is "sufficient" human evidence to establish a causal association between human exposure and the subsequent occurrence of developmental toxicity manifested by death of the conceptus (embryo or fetus), or structural or functional birth defects. This category (Human Developmental Toxicant) is comparable to category 1 of the EEC and categories D and X of FDA, except that these guidelines are limited to teratogens. This category is also comparable to the category "definitive evidence for human developmental toxicity" proposed by EPA.

(ii) *Probable Human Developmental Toxicant.* A substance is considered a "probable human developmental toxicant" if there is "limited" human evidence or "sufficient" animal evidence to establish a causal association between human exposure and subsequent occurrence of developmental toxicity. This group [Probable Human Developmental Toxicant] is comparable to the category "adequate evidence for human developmental toxicity" proposed by EPA. This category is also comparable to category 2 of the EEC and category A1 of FDA, except that these guidelines are limited to teratogens.

(iii) *Possible Human Developmental Toxicant.* A substance is considered a "possible human developmental toxicant" if there is "limited" animal evidence, in the absence of human data, or in the presence of inadequate human data, or which does not fall into any other group, to establish a causal association between human exposure and subsequent occurrence of developmental toxicity. EEC, FDA, and EPA have not developed a category comparable to this group. The Commission believes that data from well planned animal studies are important to consider even though they may provide only limited evidence of developmental toxicity.

(3) *Male Reproductive Toxicants.* Male reproductive toxicants can be grouped into the following different categories based on evidence obtained from human or animal studies.

(i) *Known Human Male Reproductive Toxicant.* A substance is considered a "known human male reproductive toxicant" if there is "sufficient" human evidence to establish a causal association between human exposure and the adverse effects on male reproductive main endpoints which are mating ability, fertility, and prenatal and postnatal development of the conceptus. This category is comparable to the one termed "Known Positive" in the EPA guidelines on male reproductive risk assessment.

(ii) *Probable Human Male Reproductive Toxicant.* A substance is considered a "probable human male reproductive toxicant" if there is "limited" human evidence or "sufficient" animal evidence to establish a causal association between human exposure and the adverse effects on male reproductive main endpoints. This category is comparable to the one termed "Probable Positive" in the EPA guidelines on male reproductive risk assessment. However, the EPA category is based only on sufficient animal evidence. CPSC believes that limited human evidence is also sufficient for a chemical to be placed in this category.

(iii) *Possible Human Male Reproductive Toxicant.* A substance is considered a "possible human male reproductive toxicant" if there is limited animal evidence, in the absence of human data, or in the presence of inadequate human data, or which does not fall into any other group, to establish a causal association between human exposure and adverse effects on male reproductive main endpoints. This category is comparable to the one termed "Possible Positive A" in the EPA guidelines on male reproductive risk assessment. EPA proposes to use either limited human or limited animal evidence data to classify a toxicant as a "Possible Positive A" toxicant. As described above, CPSC would elevate limited human evidence to the category "Probable Human Male Reproductive Toxicant."

(4) *Female Reproductive Toxicants.* Female reproductive toxicants can be grouped into the following different categories based on evidence obtained from human or animal studies. EPA has proposed guidelines for assessing female reproductive risk but has not yet proposed a specific system for categorization of female reproductive toxicants.

(i) *Known Human Female Reproductive Toxicant.* A substance is considered a "known human female reproductive toxicant" if there is "sufficient" human evidence to establish a causal association between human exposure and adverse effects on female reproductive function such as mating ability, fertility, and prenatal and postnatal development of the conceptus.

(ii) *Probable Human Female Reproductive Toxicant.* A substance is considered a "probable human female reproductive toxicant" if there is "limited" human evidence or "sufficient" animal evidence to establish a causal association between human exposure and adverse effects on female reproductive function.

(iii) *Possible Human Female Reproductive Toxicant.* A substance is considered a "possible human female reproductive toxicant" if there is "limited" animal evidence, in the absence of human data, or in the presence of inadequate human data, or which does not fall into any other group, to establish a causal association between human exposure and adverse effects on female reproductive function.

(d) *Other Subjects Related to the Determination that a Substance is Toxic.* Under the FHSA, for a toxic substance to be considered hazardous, it must not only have the potential to be hazardous but there must also be the potential that persons are exposed to the substance, that the substance can enter the body, and that there is a significant risk of an adverse health effect associated with the customary handling and use of the substance. Under these guidelines, existence of an adverse health effect means that such exposure is above the "acceptable daily

intake" ("ADI"). The ADI is based on the risks posed by the substance, and whether they are acceptable under the FHSA. This section addresses those issues by providing guidelines concerning assessment of exposure, assessment of bioavailability, determination of acceptable risks and the ADI to children and adults, and assessment of risk.

(1) *Assessment of Exposure.* An exposure assessment may comprise a single exposure scenario or a distribution of exposures. Reasonably foreseeable use, as well as accidental exposure, should be taken into consideration when designing exposure studies. The following guidelines should be used in the assessment of exposure.

(i) *Inhalation.* Inhalation studies to assess exposure should be reliable studies using direct monitoring of populations, predictions of exposure through modeling, or surrogate data.

(A) *Direct Monitoring.* Populations to be monitored should be selected randomly to be representative of the general population, unless the exposure of a particular subset population is the desired goal of the assessment. The monitoring technique should be appropriate for the health effect of interest.

(B) *Modeling.* Predictions of exposure to a chemical using mathematical models can be based on physical and chemical principles, such as mass balance principles. Mass balance models should consider the source strength of the product of interest, housing characteristics, and ambient conditions likely to be encountered by the studied population.

(C) *Surrogate Data.* Surrogate data should only be used when data concerning the chemical of interest are sparse or unavailable and when there is a reasonable assurance that the surrogate data will accurately represent the chemical of interest.

(ii) *Oral Ingestion.* Oral ingestion studies may involve direct monitoring of sources of chemicals as well as laboratory simulations. The estimation of exposure from ingestion of chemicals present in consumer products is predicted based upon estimates of use of the product and absorption of the chemical from the gastrointestinal tract. The following criteria should be established for laboratory simulations to estimate exposure:

(A) A simulant or range of simulants should be carefully selected to mimic the possible range of conditions which occur in humans, such as full and empty stomachs, or various saliva compositions at different times of the day.

(B) The mechanical action to which a product is submitted must be chosen to represent some range of realistic conditions to which a human may subject the product.

(iii) *Dermal Exposure.* (A) Dermal exposure involves estimating the amount of substance contacting the skin. This may involve experiments measuring the amount of material leached from a product contacting a liquid layer which interfaces with the skin, or the amount of substance which migrates from a product (in solid or liquid form) which is in contact with the skin.

(B) Parameters to be considered include: Surface area of the skin contacted, duration of contact, frequency of contact, and thickness of a liquid interfacial layer.

(2) *Assessment of Bioavailability.* (i) The need to consider bioavailability in estimating the risk from use of a product containing a toxic substance only arises when it is anticipated that the absorption characteristics of a substance to which there is human exposure will differ from those characteristics for the substance tested in the studies used to define the dose-response relationship.

(ii) In determining the need to assess bioavailability, the factors to be examined include:

(A) The physical or chemical form of the substance,

(B) The route of exposure (inhalation, ingestion, or through the skin),

(C) The presence of other constituents in the product which interfere with or alter absorption of the toxic substance, and

(D) Dose.

(3) *Assessment of Risk.* This section on quantitative risk assessment applies to estimates of risk for substances that are toxic by reason of their carcinogenicity.

(i) Generally, the study leading to the highest risk should be used in the risk assessment; however, other factors may influence the choice of study.

(ii) Risk should be based on the maximum likelihood estimate from a multistage model (such as Global83 or later version) unless the maximum likelihood estimate is not linear at low dose, in which case the 95% upper confidence limit on risk should be used.

(iii) For systemic carcinogens, if estimates of human risk are made based on animal data, a factor derived from dividing the assumed human weight (70 kg) by the average animal weight during the study and taking that to the ⅓ power should be used. There is the possibility that this factor may be changed, using the ¼ power instead of the ⅓ power, as part of a unified Federal regulatory approach. If such an approach is adopted, it will apply here.

(iv) When dose is expressed as parts per million, and the carcinogen acts at the site of contact, humans and animals exposed to the same amount for the same proportion of lifetime should be assumed to be equally sensitive.

(v) If no experimental study having the same route of exposure as that anticipated for human use of a substance is available, a study by another route of exposure may be used. Pharmacokinetic methods may be used if sufficient data are available.

(vi) When exposure scenarios are different from those used in the underlying study upon which estimates of risk are based, proportionality should be applied. If pharmacokinetic methods are used to adjust for risks at high versus low exposure levels, level-time measures should not be combined without taking the non-linearity into account.

(4) *Acceptable Risks.*—(i) *ADI for Carcinogens.* The maximum acceptable daily intake ("ADI") is that exposure of a toxic (by virtue of its carcinogenicity) substance that is estimated to lead to a lifetime excess risk of one in a million. Exposure refers to the anticipated exposure from normal lifetime use of the product, including use as a child as well as use as an adult.

(ii) *ADI for Neurotoxicological and Developmental/Reproductive Agents.* Due to the difficulties in using a numerical risk assessment method to determine risk for neurotoxicological or developmental/reproductive toxicants, the Commission is using a safety factor approach, as explained below.

(A) *Human Data.* If the hazard is ascertained from human data, a safety factor of ten will be applied to the lowest No Observed Effect Level ("NOEL") seen among the relevant studies. If no NOEL can be determined, a safety factor of 100 will be applied to the Lowest Observed Effect Level ("LOEL"). Both the NOEL and LOEL are defined in terms of daily dose level.

(B) *Animal Data.* If the hazard is ascertained from animal data, a safety factor of one hundred will be applied to the lowest NOEL. If no NOEL can be determined, a safety factor of one thousand will be applied to the lowest LOEL. Both the NOEL and LOEL are defined in terms of daily dose level.

3. Section 1500.3(c)(2) is amended by revising paragraph (c)(2) introductory text, redesignating paragraphs (c)(2) (i) through (iii) as paragraphs (c)(2)(i) (A) through (C) and adding new paragraphs

(c)(2)(i) introductory text and (c)(2)(ii) to read as follows:

§ 1500.3 Definitions.

* * * * *

(c) * * *

(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. The following categories are not intended to be inclusive.

(i) *Acute toxicity.* "Toxic" means any substance that produces death within 14 days in half or more than half of a group of:

(ii) *Chronic toxicity.* A substance is toxic because it presents a chronic hazard if it falls into one of the following categories. (For additional information see the chronic toxicity guidelines at 16 CFR 1500.135.)

(A) *For Carcinogens.* A substance is toxic if it is or contains a known or probable human carcinogen.

(B) *For Neurotoxicological Toxicants.* A substance is toxic if it is or contains a known or probable human neurotoxin.

(C) *For Developmental or Reproductive Toxicants.* A substance is toxic if it is or contains a known or probable human developmental or reproductive toxicant.

4. Section 1500.14 is amended by adding a new paragraph (b)(8) to read as follows:

§ 1500.14 Products requiring special labeling under section 3(b) of the Act.

(b) * * * * *

(8) *Art materials.*

Note: The Labeling of Hazardous Art Materials Act ("LHAMA"), 15 U.S.C. 1277 (Pub. L. 100-695, enacted November 18, 1988) provides that, as of November 18, 1990, "the requirements for the labeling of art materials set forth in the version of the standard of the American Society for Testing and Materials ["ASTM"] designated D-4236 that is in effect on [November 18, 1988] * * * shall be deemed to be a regulation issued by the Commission under section 3(b)" of the Federal Hazardous Substances Act, 15 U.S.C. 1262(b). For the convenience of interested persons, the Commission is including the requirements of ASTM D-4236 in paragraph (b)(8)(i) of this section, along with other requirements (stated in paragraph (b)(8)(ii) of this section) made applicable to art materials by the LHAMA. The substance of the requirements specified in LHAMA became effective on November 18, 1990, as mandated by Congress.

(i) *ASTM D-4236.*—(A) *Scope.*—(*1*) This section describes a procedure for developing precautionary labels for art materials and provides hazard and precautionary statements based upon knowledge that exists in the scientific and medical communities. This section concerns those chronic health hazards known to be associated with a product or product component(s), when the component(s) is present in a physical form, volume, or concentration that in the opinion of a toxicologist (see paragraph (b)(8)(i)(B)(*11*) of this section) has the potential to produce a chronic adverse health effect(s).

(*2*) This section applies exclusively to art materials packaged in sizes intended for individual users of any age or those participating in a small group.

(*3*) Labeling determinations shall consider reasonably foreseeable use or misuse.

(*4*) Manufacturers or repackagers may wish to have compliance certified by a certifying organization. Guidelines for a certifying organization are given in paragraph (b)(8)(i)(H) of this section.

(B) Descriptions of Terms Specific to This Standard.—(*1*) Art material or art material product—any raw or processed material, or manufactured product, marketed or represented by the producer or repackager as intended for and suitable for users as defined herein.

(*2*) Users—artists or crafts people of any age who create, or recreate in a limited number, largely by hand, works which may or may not have a practical use, but in which aesthetic considerations are paramount.

(*3*) Chronic adverse health effect(s)—a persistent toxic effect(s) that develops over time from a single, prolonged, or repeated exposure to a substance. This effect may result from exposure(s) to a substance that can, in humans, cause sterility, birth defects, harm to a developing fetus or to a nursing infant, cancer, allergenic sensitization, damage to the nervous system, or a persistent adverse effect to any other organ system.

(*4*) chronic health hazard(s) (hereafter referred to as "chronic hazard")—a health risk to humans, resultant from exposure to a substance that may cause a chronic adverse health effect.

(*5*) Analytical laboratory—a laboratory having personnel and apparatus capable of performing quantitative or qualitative analyses of art materials, which may yield information that is used by a toxicologist for evaluation of potentially hazardous materials.

(*6*) Label—a display of written, printed, or graphic matter upon the immediate container of any art material product. When the product is unpackaged, or is not packaged in an immediate container intended or suitable for delivery to users, the label can be a display of such matter directly upon the article involved or upon a tag or other suitable labeling device attached to the art material.

(*7*) Producer—the person or entity who manufactures, processes, or imports an art material.

(*8*) Repackager—the person or entity who obtains materials from producers and without making changes in such materials puts them in containers intended for sale as art materials to users.

(*9*) Sensitizer—a substance known to cause, through an allergic process, a chronic adverse health effect which becomes evident in a significant number of people on re-exposure to the same substance.

(*10*) Toxic—applies to any substance that is likely to produce personal injury or illness to humans through ingestion, inhalation, or skin contact.

(*11*) Toxicologist—an individual who through education, training, and experience has expertise in the field of toxicology, as it relates to human exposure, and is either a toxicologist or physician certified by a nationally recognized certification board.

(*12*) Bioavailability—the extent that a substance can be absorbed in a biologically active form.

(C) Requirements.—(*1*) The producer or repackager of art materials shall submit art material product formulation(s) or reformulation(s) to a toxicologist for review, such review to be in accordance with paragraph (b)(8)(i)(D) of this section. The toxicologist shall be required to keep product formulation(s) confidential.

(*2*) Unless otherwise agreed in writing by the producer or repackager, no one other than the toxicologists shall have access to the formulation(s); except that the toxicologists shall furnish a patient's physician, on a confidential basis, the information necessary to diagnose or treat cases of exposure or accidental ingestion.

(*3*) The producer or repackager, upon advice given by a toxicologist in accordance with paragraph (b)(8)(i)(D) of this section and based upon generally accepted, well-established evidence that a component substance(s) is known to cause chronic adverse health effects adopt precautionary labeling in accordance with paragraph (b)(8)(i)(E) of this section.

(*4*) Labeling shall conform to any labeling practices prescribed by federal and state statutes or regulations and shall not diminish the effect of required acute toxicity warnings.

(*5*) The producer or repackager shall supply a poison exposure management information source the generic formulation information required for dissemination to poison control centers or shall provide a 24-hour cost-free

telephone number to poison control centers.

(6) The producer or repackager shall have a toxicologist review as necessary, but at least every 5 years, art material product formulation(s) and associated label(s) based upon the then-current, generally accepted, well-established scientific knowledge.

(7) Statement of Conformance—"Conforms to ASTM Practice D-4236," or "Conforms to ASTM D-4236," or "Conforms to the health requirements of ASTM D-4236." This statement may be combined with other conformance statements. The conformance statement should appear whenever practical on the product; however, it shall also be acceptable to place the statement on one or more of the following:

(*i*) The individual product package,

(*ii*) a display or sign at the point of purchase,

(*iii*) separate explanatory literature available on requirements at the point of purchase,

(*iv*) a response to a formal request for bid or proposal.

(D) Determination of Labeling.—(*1*) An art material is considered to have the potential for producing chronic adverse health effects if any customary or reasonably foreseeable use can result in a chronic hazard.

(*2*) In making the determination, a toxicologist(s) shall take into account the following:

(*i*) Current chemical composition of the art material, supplied by an analytical laboratory or by an industrial chemist on behalf of a manufacturer or repackager.

(*ii*) Current generally accepted, well-established scientific knowledge of the chronic toxic potential of each component and the total formulation.

(*iii*) Specific physical and chemical form of the art material product, bioavailability, concentration, and the amount of each potentially chronic toxic component found in the formulation.

(*iv*) Reasonably foreseeable uses of the art material product as determined by consultation with users and other individuals who are experienced in use of the material(s), such as teachers, or by market studies, unless such use information has previously been determined with respect to the specific art material(s) under review.

(*v*) Potential for known synergism and antagonism of the various components of the formulation.

(*vi*) Potentially chronic adverse health effects of decomposition or combustion products, if known, from any reasonably foreseeable use of the hazardous art material product.

(*vii*) Opinions of various regulatory agencies and scientific bodies, including the International Agency for Research on Cancer and the National Cancer Institute, on the potential for chronic adverse health effects of the various components of the formulation.

(*3*) Based upon the conclusion reached in conformance with review determinations set forth herein, the toxicologist(s) shall recommend precautionary labeling consistent with paragraph (b)(8)(i)(E) of this section.

(E) Labeling Practices.—(*1*) Signal Word.—(*i*) When a signal word for an acute hazard(s) is mandated and a chronic hazard(s) exists, the signal word shall be that for the acute hazard.

(*ii*) When only a chronic hazard(s) exists, the signal word WARNING shall be used.

(*iii*) The signal word shall be prominently visible and set in bold capitals in a size equal to or greater than the statement of potential chronic hazards.

(*2*) List of Potentially Chronic Hazards—Potentially chronic hazards, as determined under the procedures of paragraph (b)(8)(i)(D) of this section, shall be stated substantially in accordance with the statements listed in paragraph (b)(8)(i)(F) of this section. Potentially chronic hazards noted shall be those that are clinically significant and that might be expected with any reasonably foreseeable use of the art material. The hazards should be grouped in the order of relative descending severity.

(*3*) Name of Chronically Hazardous Component(s)—All components and known decomposition products of the formulation with a potential for chronic hazards, as determined under the procedures of paragraph (b)(8)(i)(D) of this section, shall be listed prominently. Generically equivalent names may be used.

(*4*) Safe Handling Instructions—Appropriate precautionary statements as to work practices, personal protection, and ventilation requirements shall be used substantially conforming with those listed in paragraph (b)(8)(i)(G) of this section.

(*5*) List of Sensitizing Components—To protect users from known sensitizers found within art materials, each label shall contain a list of those sensitizers present in sufficient amounts to contribute significantly to a known skin or respiratory sensitization.

(*6*) Combined Statement—If an art material contains more than one component capable of causing a chronic adverse health effect, or if a single chemical can cause several different chronic adverse health effects, the potential effects may be combined into one statement.

(*7*) Information Sources—The precautionary label shall contain a statement identifying a source for additional health information substantially in conformance with one of the phrases listed below:

(*i*) For more health information—(24 hour cost-free U.S. telephone number).

(*ii*) Contact a physician for more health information, or

(*iii*) Call your local poison control center for more health information.

(*8*) Labeling Content, Product Size—Any art material product in a container larger in size than one fluid ounce (30 ml) (if the product is sold by volume) or one ounce net weight (28 g) (if the product is sold by weight) shall have full precautionary labeling, as described in paragraph (b)(8)(i) (E) of this section. Any art material product in a container equal to or smaller than one fluid ounce or one ounce net weight shall have a label that includes a signal word in conformance with paragraph (b)(8)(i)(E)(*1*) of this section and a list of potentially harmful or sensitizing components in conformance with paragraphs (b)(8)(i)(E) (*3*) and (*5*) of this section.

(*9*) The information described in paragraph (b)(8)(i)(E) of this section must appear on:

(*i*) The outside container or wrapper, if any, unless it is easily legible through the outside container or wrapper and

(*ii*) All accompanying literature where there are directions for use, written or otherwise. Where a product that requires warning labels under paragraphs (b)(8)(i) (D) and (E) of this section is packed within a point-of-sale package that obscures the warning statement(s), the point-of-sale package shall carry the signal word conforming to paragraph (b)(8)(i)(E)(*1*) and the following wording: "Contains: (list hazardous product(s)) that may be harmful if misused. Read cautions on individual containers carefully. Keep out of the reach of children."

(*10*) Statements required under paragraphs (b)(8)(i) (D) and (E) of this section must be in the English language and located prominently in conspicuous and legible type in contrast by topography, layout, or color with other printed matter on the label.

(*11*) Supplemental Information—Where appropriate, more detailed information that relates to chronic hazard(s), such as physical properties, decomposition products, detailed safety instructions, or disposal recommendations, shall be included in supplemental documents, such as

Material Safety Data Sheets, technical brochures, technical data sheets etc.

(F) chronic Hazard Statements

MAY CAUSE STERILITY.
CONTACT MAY CAUSE PERMANENT EYE DAMAGE.
MAY BE HARMFUL BY BREATHING VAPORS/DUSTS.
MAY BE HARMFUL IF SWALLOWED.
MAY BE HARMFUL BY SKIN CONTACT.
MAY PRODUCE BIRTH DEFECTS IN THE DEVELOPING FETUS.
MAY BE EXCRETED IN HUMAN MILK.
MAY CAUSE HARM TO THE NURSING INFANT.
CANCER AGENT! EXPOSURE MAY PRODUCE CANCER.
CANCER AGENT BASED ON TESTS WITH LABORATORY ANIMALS.
POSSIBLE CANCER AGENT BASED ON TESTS WITH LABORATORY ANIMALS.
MAY PRODUCE ALLERGIC REACTION BY INGESTION/INHALATION/SKIN CONTACT.
MAY PRODUCE NUMBNESS OR WEAKNESS IN THE EXTREMITIES.
EXPOSURE MAY CAUSE (SPECIFY THE ORGAN(S)) DAMAGE.
HEATING/COMBUSTION MAY CAUSE HAZARDOUS DECOMPOSITION PRODUCTS.

(G) Precautionary Statements

Keep out of reach of children.
When using do not eat, drink, or smoke.
Wash hands immediately after use.
Avoid inhalation/ingestion/skin contact.
Avoid fumes from combustion.
Keep container tightly closed when not in use.
Store in well-ventilated area.
Wear protective clothing (specify type).
Wear protective goggles/face shield.
Wear NIOSH-certified mask for dusts/mists/fumes.
Wear NIOSH-certified respirator with an appropriate cartridge for (specify).
Wear NIOSH-certified supplied-air respirator.
Use window exhaust fan to remove vapors and ensure adequate cross ventilation. (Specify explosion-proof if necessary.)
Do not heat above (specify temperature) without adequate ventilation.
Use (specify type) local exhausting hood.
Do not use/mix with (specify material).

(ii) The following shall apply with respect to the standard for art materials set forth in § 1500.14(b)(8)(i).

(A) The term *art material or art material product* shall mean any substance marketed or represented by the producer or repackager as suitable for use in any phase of the creation of any work of visual or graphic art of any medium. The term does not include economic poisons subject to the Federal Insecticide, Fungicide, and Rodenticide Act or drugs, devices, or cosmetics subject to the Federal Food, Drug, and Cosmetics Act.

(B) The standard referred to in paragraph (b)(8)(i) of this section applies to art materials intended for users of any age.

(C) Each producer or repackager of art materials shall describe in writing the criteria used to determine whether an art material has the potential for producing chronic adverse health effects. Each producer or repackager shall submit, to the Commission's Division of Regulatory Management, Consumer Product Safety Commission, Washington, DC 20207, the written description of the criteria described above and a list of art materials that require hazard warning labels under this section. Upon request of the Commission, a producer or repackager shall submit to the Commission product formulations.

(D) All art materials that require chronic hazard labeling pursuant to this section must include on the label the name and United States address of the producer or repackager of the art materials, an appropriate United States telephone number that can be contacted for more information on the hazards requiring warning labels under this section, and a statement that such art materials are inappropriate for use by children.

(E) If an art material producer or repackager becomes newly aware of any significant information regarding the hazards of an art material or ways to protect against the hazard, this new information must be incorporated into the labels of such art materials that are manufactured after 12 months from the date of discovery. If a producer or repackager reformulates an art material, the new formulation must be evaluated and labeled in accordance with the standard set forth § 1500.14(b)(8)(i).

(F) In determining whether an art material has the potential for producing chronic adverse health effects, including carcinogenicity and potential carcinogenicity, the toxicologist to whom the substance is referred under the standard described above shall take into account opinions of various regulatory agencies and scientific bodies, including the U.S. Consumer Product Safety Commission (CPSC), the U.S. Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC).

(iii) Pursuant to the LHAMA, the Commission has issued guidelines which, where possible, specify criteria for determining when any customary or reasonably foreseeable use of an art material can result in a chronic hazard. These guidelines include criteria for determining when art materials may produce chronic adverse effects in children and adults, criteria for determining which substances contained in art materials have the potential for producing chronic adverse effects and what those effects are, criteria for determining the bioavailability of chronically hazardous substances contained in art materials when the products are used in a customary or reasonably foreseeable manner, and criteria for determining acceptable daily intake levels for chronically hazardous substances contained in art materials. Because these guidelines apply to hazardous substances in general as well as to hazardous substances in art materials, the guidelines are set forth in § 1500.135 and a definition of "chronic toxicity" is provided in § 1500.3(c)(2)(ii) as part of supplementation of the term "toxic" in section 2(q) of the FHSA.

Appendix A to § 1500.14(b)(8)—Guidelines for a Certifying Organization (Not Mandatory)

(a) The term "certifying organization," as used in this paragraph, refers to an organization or an institute that, after assuring that all provisions are met, certifies that an art material does conform to the labeling requirements of this practice.

(b) The certifying body may be funded by member manufacturers, but should include users or their representatives, as well as manufacturers' chemists, on its technical and certifying committees.

(c) Representative samples of art materials, labeled as conforming to this section and bought at retail, should be analyzed at random and from time to time by an analytical laboratory to ensure they are the same as the formulation used by the toxicologist(s) for determining labeling requirements.

(d) The methods used by the toxicologist(s) in review and determination of the need and content of precautionary labeling for potentially chronic adverse health effects should be periodically reviewed by an advisory board composed of not less than three or more than five toxicologists, at least one of whom is certified in toxicology by a nationally recognized certification board.

(e) In cases where there is disagreement by participating producers or participating users, with the determination of the toxicologist(s), there should be a method whereby the toxicologist's decision can be presented to the advisory board of toxicologists for arbitration.

Dated: September 22, 1992.

Sadye E. Dunn,

Secretary, Consumer Product Safety Commission.

List of References

The following documents contain information relevant to this rulemaking proceeding and form the basis for the proposed guidelines and definition. They are available for inspection at the Office of the Secretary, Consumer Product Safety Commission, room 428, 5401 Westbard Avenue, Bethesda, Maryland:

1. Memorandum from Lakshmi C. Mishra, Senior Toxicologist, to Sandra Eberle, Program Manager, EXPB, dated October 5, 1990, entitled Criteria for Determining if a Substance is Toxic on the Basis of Carcinogenicity.

2. Memorandum from Lakshmi C. Mishra, Senior Toxicologist, to Sandra Eberle, Program Manager, EXPB, dated October 5, 1990, entitled Criteria for Determining if a Substance is Toxic on the Basis of Neurotoxicity.

3. Memorandum from Vishnudutt D. Purohit, HSHE, to Sandra Eberle, Program Manager, EXPB, dated November 15, 1990, entitled Guidelines for Identification and Classification of Developmental and Reproductive Toxicants in Consumer Products.

4. Memorandum from Warren K. Porter, Jr., Director, HSHL, to Sandra Eberle, Program Manager, EXPB, dated November 15, 1990, entitled Exposure Assessment Guidelines.

5. Memorandum from Valentine H. Schaeffer, HSHE, to Sandra Eberle, Program Manager, EXPB, dated October 5, 1990, entitled Guidelines for Assessing Bioavailability of Chronically Hazardous Substances Found in Consumer Products.

6. Memorandum from Murray S. Cohn, Director, HSHE, to Sandra Eberle, Program Manager, EXPB, dated October 5, 1990, entitled FHSA Risk Assessment Guidelines.

7. Memorandum from Murray S. Cohn, Director, HSHE, to Sandra Eberle, Program Manager, EXPB, dated October 5, 1990, entitled Acceptable Risks to Children and Adults.

8. Memorandum from Michael A. Babich, Project Manager, dated March 24, 1992, entitled Responses to Public Comments and Draft Final Rule on the Labeling of Art Materials and Other Products.

The following documents are referenced in the Memoranda listed above and may have been referred to in the preamble of this rulemaking. They are listed here for the convenience of the reader.

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[FR Doc. 92–23659 Filed 10–8–92; 8:45 am]

BILLING CODE 6355–01–M