(c) The words that are in capital letters in the warning statement set forth in paragraph (b) of this section should be printed on the main (front) panel or panels of the container in capital letters of the type size specified in §1500.121(c). The balance of the cautionary information may appear together on another panel provided the front panel bears a statement such as ''Read carefully other cautions on _____ panel,'' the blank being filled in with the identification of the specific label panel bearing the balance of the cautionary labeling. It is recommended that a borderline be used in conjunction with the cautionary labeling.

(d) If an article has additional hazards, or contains ingredients listed in §1500.14 as requiring special labeling, appropriate additional front and rear panel precautionary labeling is required.

(e) Since the Commission has issued a regulation banning under the Consumer Product Safety Act extremely flammable contact adhesives covered by this labeling regulation (sec. 16 CFR part 1302), paragraphs (a), (b), (c) and (d) of this section are revoked as to the subject products after June 13, 1978.

[38 FR 27012, Sept. 27, 1973, as amended at 42 FR 63742, Dec. 19, 1977]

§ 1500.134 Policy on first aid labeling for saline emesis.

(a) This section states the Consumer Product Safety Commission's policy concerning first aid instructions for the use of a salt solution to induce vomiting (saline emesis) in the event of ingestion of hazardous substances.

(b) In many cases where hazardous substances are ingested, the recommended first aid instructions for inducing vomiting have contained a statement that this should be accomplished by drinking a solution of salt (sodium chloride) in warm water. At one time, this direction was considered medically acceptable. However, the Commission has obtained information showing that the instruction to perform saline emesis is no longer appropriate. This is because the use of salt to induce vomiting can cause severe hypernatremia (salt poisoning) with potentially toxic effects, particularly in children 5 years old or younger, the age group most often involved in accidental poisonings. In view of the availability of safer and more effective emetics such as ipecac syrup, the Commission no longer recommends a direction to perform saline emesis as a first aid direction for inducing vomiting.

(c) The Commission believes that, for products for which directions for saline emesis have been given in the past, ipecac syrup, U.S.P., is the most appropriate emetic, unless a particular contraindication exists in connection with any particular hazardous substance.

(d) The Commission wishes to emphasize that this policy does not require that any specific first aid instruction or wording be used. Where appropriate, the label may include directions (1) that the victim immediately contact a doctor or poison control center and/or (2) that vomiting be induced using methods other than salt. It is, of course, the manufacturer's responsibility to insure that the label provides enough information in addition to first aid instructions to fulfill all other labeling required by statute or regulation.

(Sec. 30(a), 86 Stat. 1231 (15 U.S.C. 2079(a)))

[43 FR 33704, Aug. 1, 1978]

§ 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.

[57 FR 46665, Oct. 9, 1992]

§ 1500.210 Responsibility.

The provisions of these regulations (16 CFR subchapter C of chapter II) with respect to the doing of any act shall be applicable also to the causing of such act to be done.