

Appendix III

FEDERAL REGULATION OF CARCINOGENIC SUBSTANCES

INTRODUCTION

Federal authorities to regulate carcinogenic substances are usually contained within statutory provisions for regulating toxicity in general. With two major exceptions, the relevant statutes do not specifically mention carcinogenicity or cancer. These exceptions are the Federal Food, Drug, and Cosmetic Act and the Toxic Substances Control Act. Both Acts contain provisions that relate directly to carcinogens, and both specify procedures for regulating carcinogenicity that are distinct from those for general toxicity.

Nine statutes are important in the regulation of carcinogenic substances. One of these, the Food, Drug, and Cosmetic Act, generally takes precedence over other Federal laws for the carcinogenicity of substances that may be ingested. Health hazards in the workplace are covered by the Occupational Safety and Health Act. A third class of substances, those to which consumers are likely to be exposed (other than foods, drugs, cosmetics, and other excluded substances), is regulated by the Consumer Product Safety Act and the Federal Hazardous Substances Act. Four statutes administered by the Environmental Protection Agency (EPA) cover specific areas of the physical environment: the Clean Air Act; the Water Pollution Control Act; the Safe Drinking Water Act; and the Federal Insecticide, Fungicide, and Rodenticide Act. The Environmental Protection Agency also administers the Toxic Substances Control Act, a law designed to fill in gaps in the regulatory coverage of toxic substances in the environment.

Of these laws, only the Food, Drug, and Cosmetic Act contains provisions such as the "Delaney clause" that allow no regulatory discretion. When a substance regulated by one of these provisions is found to be a carcinogen, it must be banned. No other law, not even that for hazards to consumers, mandates such specific obligatory action. Thus the laws are not consistent with each other.

The various laws also differ in their approaches to risk/benefit analysis. Some, such as the Toxic Substances Control Act, explicitly require the balancing of health risks against economic and other public impacts of regulation. Others permit such analysis, but do not require it. The Food, Drug, and Cosmetic Act requires it in some cases and forbids it in others, depending on the types of substances in question.

Summaries and discussion of the statutory authorities for the four classes of substances (ingested, workplace, consumer products, and environmental) follow.

FDA REGULATION OF INGESTED SUBSTANCES

Humans ingest a variety of substances that are under the control of the Food and Drug Administration (FDA): as foods, food additives, color additives, drugs, vitamins, and minerals; as residues from animal feed, animal drugs, and pesticides; and even as cosmetics. The statutes and regulations used by FDA to control these substances vary with the form of ingestion.

Statutes referred to are from the Federal Food, Drug, and Cosmetic Act, as amended; Title 21, United States Code (copy dated October 1976). Regulations are quoted from Title 21, Code of Federal Regulations,* chapter 1. Unless otherwise noted, “section” references are to the statutes.

A. Food and Substances in Foods

(1) Definitions

(a) The term “food” means

(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article [section 201 (f)].

(b) A Food Additive is any substance

the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food [section 201(s)].

(i) A Food Additive under law is thus not simply anything added to food. Certain substances that are added to food are exempted from the statutory provisions relating to Food Additives but are still subject to the other provisions of the Act (such as section 402, the section on adulterated foods). The definition of Food Additive is restricted to substances “not generally recognized . . . to be safe under the conditions of its intended use.” [This qualification is the basis for the Generally Recognized As Safe (GRAS) List.] The section then continues: “except that such term [Food Additive] does not include:

- (1) a pesticide chemical in or on a raw agricultural commodity; or
- (2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or
- (3) a color additive; or
- (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act . . . or [other Acts]. [This last phrase is the so-called “prior sanction” clause.]
- (5) a new animal drug [section 201(s)].

(ii) Thus, any substance that fits the definition of a Food Additive given above and which is not on the GRAS list, for which “prior sanction” has not been granted, or which does not fit any of the other excluded

*Numbers of sections are those in use as of February 1977.

categories is a Food Additive and is specifically subject to regulation under section 409 of the Act.

(iii) Any substance that is a Food Additive is also a Food and subject to other provisions of the Act.

(c) A Color Additive is a material that

(A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when added or applied to food, drug, or cosmetic, or to the human body or any part thereof; is capable (alone or through reaction with other substances) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring [section 201 (t)].

(2) Regulation of Food Additives

(a) [409(a)]: Once a substance is classified as a Food Additive under the strict meaning given above, it is to be deemed unsafe for the purposes of section 409(c) (3) (a) unless it has been exempted for investigational use [section 409(i)], or,

there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used [section 409(a) (2)].

In either of these cases, the Food Additive is not in violation of section 402(a), the food adulteration section, which serves as the basis for prohibiting use.

The regulation is not to be issued if a fair evaluation of the data

fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal, except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal, [section 409(c)(3)(A)]*

If a regulation is issued, FDA may set tolerance limits, specify the foods in which the Food Additive may be used and in what amounts, labeling instructions, etc.

In determining whether a regulation shall be issued, the following factors (as well as any others that are relevant) shall be considered:

- (a) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;
- (b) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet; and
- (c) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data. [section 409(c)(5)]

(b) Before a Food Additive is marketed, the petitioner has the burden of proof to show that the proposed Food Additive is safe and performs as claimed. However, once a Food Additive is on the market, with an approved regulation, a change occurs. While the *burden of proof* remains with the original petitioner, the burden of "going forward" with the *evidence* shifts to FDA. That is, FDA has the responsibility for presenting evidence that will lead to a reconsideration of a Food Additive's safety. Under the "Delaney clause," FDA's responsibility is satisfied as soon as it finds that a Food Additive is carcinogenic. When FDA proceeds under the general safety clause, it must present evidence that the Food Additive has been shown to have certain effects (e.g., toxicity) and that these effects lead to harm. The general safety clause is the portion of 409(c) (3) (A) that precedes the "Delaney clause."

(c) Action against Food Additives deemed unsafe is taken on the basis of section 402(a) (2) (c), the adulterated food section (to be described later).

(d) Other sections of the Code of Federal Regulations that are especially pertinent to food additives are excerpted below.

(i) **21 CFR 121.1*—Definitions and Interpretations**

(f) 'Common use in food' means a substantial history of consumption of a substance by a significant number of consumers in the United States. . .

* * * * *

(h) 'Scientific procedures' include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

(i) 'Safe' or 'safety' means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

(1) The probable consumption of the substance and of any substance formed in or on food because of its use.

*21 CFR 121.1 refers to Title 21 of the Code of Federal Regulations, Section 121.1. Other citations will follow this format.

(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.

(3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate. . .

* * * * *

(k) 'General recognition of safety' shall be determined in accordance with §121.3.

§121.3 Classification of a food ingredient as generally recognized as safe (GRAS).

(a) General recognition of safety maybe based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food.

(ii) 121.5—Safety factors to be considered:

In accordance with section 409(c) (5) (C) of the act, the following safety factors will be applied in determining whether the proposed use of a food additive will be safe: Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1, will be used: that is, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals.

(iii) 121.6-General principles for evaluating the safety of food additives:

(a) In reaching a decision on any petition filed under section 409 of the act, the Commissioner will give full consideration to the specific biological properties of the compound and the adequacy of the methods employed to demonstrate safety for the proposed use, and the Commissioner will be guided by the principles and procedures for establishing the safety of food additives stated in current publications of the National Academy of Sciences-National Research Council. A petition will not be denied, however, by reason of the petitioner's having followed procedures other than those outlined in the publication of the National Academy of Sciences—National Research Council if, from available evidence, the Commissioner finds that the procedures used give results as reliable as, or more reliable than, those reasonably to be expected from the use of the outlined procedures. In reaching a decision, the Commissioner will give due weight to the anticipated levels and patterns of consumption of the additive specified or reasonably inferable. For the purposes of this section, the principles for evaluating safety of additives set forth in the above-mentioned publications will apply to any substance that may properly be classified as a food additive as defined in section 201 (s) of the act.

(b) Upon written request describing the proposed use of an additive and the proposed experiments to determine its safety, the Commissioner will advise a person who wishes to establish the safety of a

food additive whether he believes the experiments planned will yield data adequate for an evaluation of the safety of the additive.

- (iv) 121.4001—Saccharin, ammonium saccharin, saccharin, calcium saccharin, and sodium saccharin (“Interim Regulation” on saccharin):

The food additives saccharin, ammonium saccharin, calcium saccharin, and sodium saccharin may be safely used as sweetening agents in food in accordance with the following conditions, if the substitution for nutritive sweeteners is for a valid special dietary purpose and is in accord with current special dietary food regulations and policies or if the use or intended use is for an authorized technological purpose other than calorie reduction:

(a) Saccharin is the chemical, 1, 2-benzisothiazolin-3-one-1, 1-dioxide, ($C_7H_5NO_3S$). The named salts of saccharin are produced by the additional neutralization of saccharin with the proper base to yield the desired salt.

(b) The food additives meet the specifications of the ‘Food Chemicals Codex.’

(c) Authority for such use shall expire when the Commissioner receives a final report and recommendations from the National Academy of Science Committee on Saccharin and publishes an order based on this report.

(d) The additives are used or intended for use as a sweetening agent only in special dietary foods, as follows:

(1) In beverages, fruit juices, drinks, and bases or mixes when prepared for consumption in accordance with directions, in amounts not to exceed 12 milligrams of the additive, calculated as saccharin, per fluid ounce,

(2) As a sugar substitute for cooking or table use, in amounts not to exceed 20 milligrams of the additive, calculated as saccharin, for each expressed teaspoon full of sugar sweetening equivalence.

(3) In processed foods, in amounts not to exceed 30 milligrams of the additive, calculated as saccharin, per serving of designated size.

(e) The additives are used or intended for use only for the following technological purposes:

(1) To reduce bulk and enhance flavors in chewable vitamin tablets, chewable mineral tablets, or combinations thereof.

(2) To retain flavor and physical properties of chewing gum.

(3) To enhance flavor of flavor chips used in nonstandardized bakery products.

(f) To assure safe use of the additives, in addition to the other information required by the act:

(1) The label of the additive and any intermediate mixes of the additive for manufacturing purposes shall bear:

(i) The name of the additive.

(ii) A statement of the concentration of the additive, expressed as saccharin, in any intermediate mix,

(iii) Adequate directions for use to provide a final food product that complies with the limitations prescribed in paragraphs (d) and (e) of this section.

(2) The label of any finished food product containing the additive shall bear:

- (i) The name of the additive.
- (ii) The amount of the additive, calculated as saccharin, as follows :
 - (a) For beverages, in milligrams per fluid ounce;
 - (b) For cooking or table use products, in milligrams per dispensing unit.
 - (c) For processed foods, in terms of the weight or size of a serving dish which shall be that quantity of the food containing 30 milligrams or less of the additive.
- (iii) When the additive is used for calorie reduction, such other labeling as is required by part 125 or §3.72 of this chapter.

(e) Listing of other pertinent Regulation sections:

<i>Section #</i>	<i>Title</i>
121.3	Eligibility for classification as GRAS
121.4	Tolerances for related food additives
121.8	Food additives in standardized foods
121.40	Affirmation of GRAS status
121.41	Determination of food additive status
125.1	Definitions and interpretations of terms [for dietary uses]
125.7	Label statements relating to nonnutritive constituents [of dietary foods]

(3) Regulation of Color Additives

(a) There are many similarities between the regulation of color additives and food additives. Any substance meeting the definition of "Color Additive" given above is to be deemed unsafe unless the Secretary of HEW has issued a regulation specifying its safe conditions of use [section 706(a)]. Without such a regulation, a color additive is to be regarded as adulterated under sections 402(c) when in foods, 501 (a) in drugs, and 601 (e) in cosmetics.

(b) The Secretary shall issue the regulation only when

the data before him establish that such use . . will be safe. . . Provided, however, that a color additive shall be deemed to be suitable and safe for the purpose of listing under this subsection for use generally in or on food, while there is in effect a published finding of the Secretary declaring such substance exempt from the term 'food additive' because of its being generally recognized by qualified experts as safe for its intended use, as provided in section 201 (s). [section 706(b) (4)].

(c) In determining safety the following factors, among others, are to be considered:

- (i) the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs, devices, or cosmetics because of the use of the additive;
- (ii) the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet;
- (iii) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data; and
- (iv) the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive, [section 706(b)(5)(A)]

(d) However, the color additive section of the Act has its own Delaney-type clause that takes precedence over the above criteria:

(B) A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal: *Provided*, that clause (i) of the subparagraph (B) shall not apply with respect to the use of a color additive as an ingredient of feed for animals which are raised for food production, if the Secretary finds that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsection (d)) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animal. [section 706 (b)(5)(B)]

(e) The Act also allows exemptions for the investigatory use of color additives section 706(f) and for the provisional listing of commercially established color additives, pending further investigation as to their safety [section 203, Title II, of Public Law 86-618],

(f) Action against color additives found to be unsafe by the provisions of section 706 is taken on the basis of adulteration. That is, the substance of which a color additive is a component will be classified as adulterated.

- (i) A drug is adulterated if it bears, contains, or is itself an unsafe color additive. [section 501 (a) (4)]
- (ii) A food is adulterated if it is, or it bears or contains, an unsafe color additive. [section 402(c)]
- (iii) A cosmetic is adulterated if it is not a hair dye and it is, or it bears or contains, an unsafe color additive. [section 601(c)]

(4) Regulation of Vitamins and Minerals

(a) Vitamins and minerals, and components of such substances, are regulated as foods unless therapeutic or other medical claims are made for the **vitamin or mineral by its sponsor**. If such claims are made, these substances are to be considered drugs and must go through the New Drug Application (NDA) process (unless they fall under the “grandfather clause” described above).

(b) Specific statutory language for vitamins and minerals deemed to be foods covers potency levels, labeling, and the like. Their safety is to be assessed by provisions relating to foods in general, not by provisions in section 411 (“Vitamins and Minerals”). For example, such vitamins and minerals are subject to section 402, adulterated foods.

(5) Regulation of Foods in General

(a) Section 301 of the Act prohibits the introduction of any adulterated or misbranded food into interstate commerce. It also prohibits the adulteration or misbranding of foods already in interstate commerce.

(b) Section 402 lists the criteria by which a food is to be deemed adulterated. The following excerpts are of particular interest for this report:

(a)(1) **If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health; or**

(2)(A) **If it bears or contains any added poisonous or added deleterious substance (other than one which is (i) a pesticide chemical in or on a raw agricultural commodity; (ii) a food additive; (iii) a color additive; or (iv) a new animal drug which is unsafe within the meaning of section 406, or (B) if it is a raw agricultural commodity and it bears or contains a pesticide chemical which is unsafe within the meaning of section 408(a); or (C), if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409: Provided, that where a pesticide chemical has been used in or on a raw agricultural commodity in conformity with an exemption granted or a tolerance prescribed under section 408 and such raw agricultural commodity has been subjected to processing such as canning, cooking, freezing, dehydrating, or milling, the residue of such pesticide chemical remaining in or on such processed food shall, notwithstanding the provisions of section 406 and 409, not be**

deemed unsafe if such residue in or on the raw agricultural commodity has been removed to the extent possible in good manufacturing practice and the concentration of such residue in the processed food when ready to eat is not greater than the tolerance prescribed for the raw agricultural commodity; or (D) if it is, or it bears or contains, a new animal drug (or conversion product thereof) which is unsafe within the meaning of section 512; or . . .

* * * * *

(c) If it is, or it bears or contains, a color additive which is unsafe within the meaning of section 706(a).

(d) If it is confectionery, and—

(1) has partially or completely imbedded therein any non-nutritive object: *Provided, that this clause shall not apply in the case of any nonnutritive object if, in the judgment of the Secretary as provided by regulations, such object is of practical functional value to the confectionery product and would not render the product injurious or hazardous to health;*

(2) bears or contains any alcohol other than alcohol not in excess of one-half of 1 per centum by volume derived solely from the use of flavoring extracts; or

(3) bears or contains any nonnutritive substance: *Provided, that this clause shall not apply to a safe nonnutritive substance which is in or on confectionery by reason of its use for some practical functional purpose in the manufacture, packaging, or storage of such confectionery if the use of the substances does not promote deception of the consumer or otherwise result in adulteration or misbranding in violation of any provision of this Act: And provided further, That the Secretary may, for the purpose of avoiding or resolving uncertainty as to the application of this clause, issue regulations allowing or prohibiting the use of particular non-nutritive substance.*"

If section 409 and, therefore 402(a) (2) (C) were deleted, 402(a) (2)(A)(ii) would also be eliminated. Food additives, like other foods, would then be covered by the general provision on food adulteration (section 402).

(c) Section 406, Tolerances for Poisonous Ingredients, has been mentioned by various individuals in regard to saccharin and other sweeteners. However, the wording of the clause indicates that if the use of a poisonous ingredient can be avoided (by good manufacturing practice or because it is not required by production), then the ingredient itself and foods that contain it are to be deemed unsafe, adulterated as per section 402(a) (2) (A). This section, which is primarily used for environmental contaminants that may get into food, states:

Any poisonous or deleterious substance added to any food, except where such substance is required in the production thereof or cannot be avoided by good manufacturing practice shall be deemed to be unsafe for purposes of the application of clause (2) (A) of section 402(a); but when such substance is so required or cannot be so avoided, the Secretary shall promulgate regulations limiting the quantity therein or thereon to such

extent as he finds necessary for the protection of public health, and any quantity exceeding the limits so fixed shall also be deemed to be unsafe for purposes of the application of clause (2) (A) of section 402(a). While such a regulation is in effect limiting the quantity of any such substance in the case of any food, such food shall not, by reason of bearing or containing any added amount of such substance, be considered to be adulterated within the meaning of clause (1) of section 402(a). In determining the quantity of such added substance to be tolerated in or on different articles of food the Secretary shall take into account the extent to which the use of such substance is required or cannot be avoided in the production of each such article, and the other ways in which the consumer may be affected by the same or other poisonous or deleterious substances.

(d) Of course, a great many other sections in the Act pertain to food regulation. Those sections relevant to the purposes of this report have, however, been described.

B. Drugs and Substances in Drugs

(1) Definitions

(a) The term "drug" means

(A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories. [section 201 (g)(1)].

(b) The term "new drug" means:

(i) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized by scientific experts] as safe and effective for use. . .

except that such a drug is not considered to be a "new drug" if it was in use under the conditions of the 1906 Pure Food and Drug Act (that is, it was permitted to be on the market before the enactment of the present (1938) Act) and is still labeled for the same conditions of use; or

(ii) Any drug recognized, as a result of scientific investigations, as safe and effective, but which has not been used "to a material extent or for a material time under such conditions [for which it is shown to be safe and effective] [section 201 (p)].

(2) The Drug Approval Process

(a) The Act, as amended, requires that no new drug may be marketed unless an application for marketing has been approved by the Secretary of HEW

[section 505(a)]. The FDA is the agency that has been assigned the responsibility for implementing this Act. The approval of an application to market a new drug is based in large measure on a demonstration of its safety and efficacy. The requirement that efficacy be demonstrated was added by the 1962 amendments to the Act. The FDA approves or disapproves a New Drug Application (or allows an existing drug to stay in the market) when it judges that the total biochemical action of the drug yields positive results that outweigh the risks and when the individual ingredients are either safe or provide benefits outweighing their risks.

(b) Section 505(i) and its implementing regulations permit exemptions for the investigational (research) use of new drugs. Any person or organization which wishes to do research on a new drug in human beings must file a "notice or claimed exemption for investigational new drug" (IND) and then wait at least 30 days. If FDA does not prohibit commencement during the 30-day period, human trials may begin. Decisions to permit research under INDs are based on criteria ensuring that human subjects are not exposed to unjustified and unnecessary safety risks.

(c) Following IND-approved research (or during it), a New Drug Application (NDA) is submitted to FDA by the organization developing the drug.

When an NDA is submitted, FDA (on the basis of criteria of safety and efficacy specified in the Act) must within 180 days approve or disapprove the application. This time limit may be extended by mutual agreement.

Section 505(d) of the Federal Food, Drug, and Cosmetic Act sets forth the six criteria to be used in not approving an application to market a new drug. Four of these criteria deal with safety and purity [section 505(d) (1) through 505(d) (4)], one deals with labeling requirements [section 505(d) (6)], and one deals with efficacy [section 505(d) (5)].

(d) Relevant parts of section 505(d):

If the Secretary finds . . . that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.

If any of these conditions hold, the Secretary shall not approve the NDA.

- (e) The term "substantial evidence" refers, in tests for efficacy, to evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof, [section 505(d)]

Safety is to be determined by "adequate tests by all methods reasonably applicable." [section 505(d)(1) and 505(d)(2)]

(f) Because safety and efficacy are separate criteria, FDA must weigh the advantages (the benefits) of the drug against the dangers (safety, risks) in deciding whether to approve an NDA or to allow approval to stand. Thus, drugs that would not meet the criteria of safety for foods may be approved because their benefits outweigh the risks. This approval is possible because the statutes for regulating drugs contain no Delaney-type clause; safety is implicitly recognized as a relative concept. A drug containing a substance, such as saccharin, would therefore, not be automatically unapproved.

(3) New Information on Risks

(a) If new information is developed or learned about the risks of a drug or a substance in a drug, FDA can take several actions. If the agency believes information to be substantial, it could issue a regulation proposing to classify the previously approved drug as a "new drug." This action requires that the evidence on safety and efficacy be reexamined and the new information taken into account. FDA may also require the sponsor of the drug to perform additional tests of its safety or efficacy.

Section 505(e) specifies that:

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) the new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Withdrawing approval automatically classifies the drug as a "new drug."

(b) When a substance that is a component of a number of drugs becomes suspected of posing risks to health, all drugs containing it can be classified as "new drugs" (after appropriate notice) as specified above. The regulations issued by FDA contain several relevant sections relating to the above points. For example,

(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time—even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread clinical use pending completion of such long-term studies. In such cases, the Food and Drug Administration may approve the new-drug application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion. The procedures required by paragraph (b) of this section will be followed in order to list such a drug in 5310.304.

(b) A proposal to require additional or continued studies with a drug for which a new-drug application has been approved may be made by the Commissioner on his own initiative or on behalf of any interested person. Prior to issuance of such a proposal, the applicant will be provided an opportunity for a conference with representatives of the Food and Drug Administration. When appropriate, investigators or other individuals may be invited to participate in the conference. Such proposal and a summary of the grounds upon which it is proposed will be published in the *Federal Register* acting on the proposal. Proposals submitted by interested persons may be refused by written notice from the Commissioner if the proposal is not supported by reasonable grounds. Upon final determination that special studies, records, and reports are required for a drug, such requirements will be published in §310.304. [section 310.303]

(c) Similar provisions apply to over-the-counter drug products, many of which contain saccharin:

An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulator action.

(a) The product is manufactured in compliance with current good manufacturing practices, as established by Parts 210, 211, 225, 266 and 229 of this chapter. . .

* * * * *

(e) The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 706 of the act and Parts 8 and 9 of this chapter.

Regulations pertaining specifically to drugs and new drugs for humans appear in 21 CFR, Parts 300-499.

(4) Regulatory Action

As stated above, no new drug may be marketed or remain on the market unless an approved NDA is in effect for that drug [section 505(a) of the Act]. Approval, once given, can be withdrawn in accord with the provisions of section 505(e), as described above. According to section 301 (d), any organization or individual that markets or continues to market an unapproved drug is in violation of section 505.

C. Regulation of Cosmetics

(1) Definitions

(a) The term "cosmetic" means:

(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap. [section 201 (i)].

(b) A cosmetic shall be deemed to be adulterated:

(a) If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual [an exception is made for coal-tar hair dyes that are properly labeled]. . .

* * * * *

(d) If its container is composed, in whole or part, of any poisonous or deleterious substance which may render the contents injurious to health.

(e) If it is not a hair dye and it is, or it bears or contains, a color additive which is unsafe within the meaning of section 706(a). [section 601].

(2) Regulation of Cosmetics

(a) Regulation of cosmetics is relevant to this study because certain cosmetics, such as lipstick or toothpaste, and substances in cosmetics may be ingested by the consumer.

(b) Action is taken against an adulterated cosmetic under the provisions of Section 301, "Prohibited Acts." The specific clauses are the same ones as those used to ban adulterated foods and drugs: Sections 301(a), (b), and (c).

D. Residues of Certain Substances

(1) Definitions

(a) Certain substances that are not deliberately ingested by humans are ingested as residues from their use in animal feeds, animal drugs, and pesticide chemicals. Animal feeds are considered to be "foods" by the Act and thus subject to the applicable portions of its chapter IV, "Foods." However, animal feeds may also contain animal drugs that could remain as a residue and thus be ingested by humans. In these cases, the residues of such animal drugs are regulated by several other sections of the statutes.

(b) The term "pesticide chemical" means

any substance which, alone, in chemical combination or in formulation with one or more other substances, is an 'economic poison' within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. secs. 135-135K) as now in force or as hereafter amended, and which is used in the production, storage, or transportation of raw agricultural commodities. [section 201 (9)]

(c) The term "new animal drug" means

any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed—

**(1) the composition of which is such that such drug is not generally recognized. . .as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; [except that any animal drug that was in the market before June 25, 1938 and subject to the 1906 Pure Food and Drug Act (and is being represented for the same indications) is not to be deemed a "new animal drug;"] or
(2) the composition of which is such that such drug, as a result of investigations to determine safety and effectiveness for use under such conditions, has become so recognized but which has not. . been used to a material extent or for a material time under such conditions. [section 201 (w)].**

(d) The term "animal feed" means

an article which is intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal. [section 201 (x)]

(2) Regulation of Animal Drugs

The definition of "drug" given in the Act also applies to drugs used in animals. The term "new drug" does not. Instead, the term "new animal drug" is used. Treatment of new animal drugs is very similar to that for new drugs. An application for a

new animal drug follows a procedure parallel to the NDA process for new human drugs, except that the new animal drug process contains a Delaney-type clause. Section 512(d) (1) lists the criteria used in approving or not approving an application to market a new animal drug. According to clause (H) of the section, an application must be refused if it is found that

such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h)), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals.

Thus, if humans will ingest any residue of a new animal drug that induces cancer in man or animal, then the new animal drug application cannot be approved. Action is taken against the drug under the provisions for an unsafe new animal drug or on animal feed containing an unsafe new animal drug [sections 501 (a) (5) and sections 501 (a) (6)]. Similarly, if an approved animal drug is found later to meet the above conditions, its approval will be rescinded under the provisions of section 512(e) (1) (B).

When a new animal drug has been approved, foods containing residues of such drug are not considered adulterated. However, if approval has not been given, such foods are deemed to be adulterated by the terms of section 402(a) (2) (D). According to this section, a food is adulterated

if it is, or it bears or contains, a new animal drug (or conversion product thereof) which is unsafe within the meaning of section 512.

In short, if no potentially carcinogenic residues (as determined by assay methods that meet the criteria of FDA) of an animal drug (or a conversion product thereof) will be ingested by humans, its safety for humans is not an issue. If noncarcinogenic residues are likely to be ingested, the animal drug (in the allowable amounts) must meet the conditions of safety of the Act. If the animal drug has been shown to be carcinogenic, no residues identifiable by prescribed assay methods are permitted,

(3) Regulation of Pesticide Residues

A food is deemed to be adulterated "if it is a raw agricultural commodity and it bears or contains a pesticide chemical which is unsafe within the meaning of section 408(a)." [section 402(a) (2) (B)] section 408 discusses "Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities":

Any poisonous or deleterious pesticide chemical, or any pesticide chemical which is not generally recognized. . . as safe for use, added to a raw agricultural commodity, shall be deemed unsafe for the purposes of the application of clause (2) of section 402(a) unless—

(1) a tolerance for such pesticide chemical in or on the raw agricultural commodity has been prescribed by the Secretary of Health, Education,

and Welfare under this section and the quantity of such pesticide chemical in or on the raw agricultural commodity is within the limits of the tolerance so prescribed; or

(2) with respect to use in or on such raw agricultural commodity, the pesticide chemical has been exempted from the requirement of a tolerance by the Secretary under this section [when a tolerance is not necessary to protect the public health]. [section 408(a)]

The responsibility for this section has been delegated to the Environmental Protection Agency, but enforcement according to section 402 remains with FDA. The Act specifies certain factors (other than general safety of the chemical) for the Secretary of HEW to consider in issuing the regulations referred to above:

The Secretary shall give appropriate consideration, among other relevant factors, (1) to the necessity for the production of an adequate, wholesome, and economical food supply; (2) to the other ways in which the consumer may be affected by the same pesticide chemical or by other related substances that are poisonous or deleterious; and (3) to the opinion of the Secretary of Agriculture as submitted with a certification of usefulness under subsection (1) of this section. [section 408(b)]

Although there is no Delaney-type clause for pesticide residues, the Act does state that:

In carrying out the provisions of this section relating to the establishment of tolerances, the Secretary may establish the tolerance applicable with respect to the use of any pesticide chemical in or on any raw agricultural commodity at zero level if the scientific data before the Secretary does not justify the establishment of a greater tolerance. [section 408(b)]

Tolerance levels relate to the amounts of residues permitted in foods that will be ingested by humans.

(4) Other Residues

- (a) Color Additives have been discussed above. Section 706(b)(5)(B) indicates that if a color additive used in animal feed were shown to be carcinogenic, its use is prohibited *unless no residue* of the color additive found its way into the human diet.
- (b) Food additives in animal feed are also subject to section 409(c)(3)(A) [the "Delaney clause"].

REGULATION OF CARCINOGENIC SUBSTANCES IN THE WORKPLACE

The purpose of the Occupational Safety and Health Act, Public Law 91-596, is to ensure working conditions as safe and healthy as possible for every working person. It is administered primarily by the Occupational Safety and Health Administration of the Department of Labor. Certain functions related to scientific research are the responsibility of the National Institute of Occupational Safety and Health of HEW.

The Act does not address carcinogenicity specifically, but rather toxicity in general. The Secretary of Labor, by promulgating a regulation, can set occupational safety and health standards for toxic substances.

Section 6(b) (5) of the Act specifies that:

The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.

A standard can specify the conditions of use "reasonably" necessary or appropriate to provide safe and healthful employment. Standards are developed on the basis of research, demonstrations, experiments, and such other information as may be appropriate. In addition to safety and health goals, other factors are considered in setting standards: feasibility, state of scientific knowledge, and experience gained under this Act and other health laws.

The Department of Labor does, however, issue regulations specifically on carcinogenic substances in the workplace. A draft of proposed regulations on exposure of workers to cancer-causing chemicals was made public in January 1977. As of July 20, 1977, this proposal remains a draft; current procedures still apply. That is, each substance suspected of or confirmed as being carcinogenic is considered individually and, depending on the available evidence, a standard specifying allowable conditions of use is issued.

Under the draft proposal, setting standards case by case would be replaced by the use of three uniform job-health standards. Each carcinogen or suspected carcinogen would be placed into one of three categories. Each category has its corresponding uniform standard (allowable exposure levels may vary depending on the substance, even within the same category).

The proposed categories are:

Category I Toxic Materials

A substance will be classified as a Category I Toxic Material ("confirmed" carcinogen) based on positive evidence found in any of the following:

1. Humans.
2. Two mammalian test species.
3. One mammalian species, if the results are replicated in the same species in a separate study.
4. A single mammalian species if the results are supported by multitest evidence of mutagenicity.

Category II Toxic Materials

A substance will be classified as Category II Toxic Material ("suspect" carcinogen) if the evidence of carcinogenicity in humans or one or more mammalian species is found by OSHA to be only "suggestive" as opposed to confirming. Such a distinction would be based on generally accepted standards of review for such scientific studies.

Category III Toxic Materials

A substance for which the evidence of carcinogenicity is found inadequate to classify as Category I or II will be classified as Category III.

When a substance is classified into category I, the Secretary of Labor is required immediately to issue an emergency standard by a regulation setting forth the allowable conditions of use. At the same time that the emergency standard is issued, a process to develop a permanent standard begins. The use of such a classified substance can be prohibited altogether. When a less dangerous alternative to the substance is available, the substance must be banned.

Placing a substance in category II initiates a process that will result in a permanent standard setting forth allowable safe uses of the substance. The Occupational Safety and Health Administration also is required to notify HEW (especially the National Cancer Institute and the National Institute of Occupational Safety and Health), EPA, and other applicable agencies that the evidence of the substance's carcinogenicity is only "suggestive" and request that the agencies engage in or stimulate further research.

The OSHA statutes do not contain any Delaney-type clause. The agency (and thus the Secretary of Labor) can set limits of exposure greater than zero for substances shown to cause cancer. Further, the draft proposal clearly states that the safety aspects of prohibition are to be balanced against technological feasibility and economic consequences.

While the Federal Food, Drug, and Cosmetic Act specifically addresses "cancer," the OSHA proposed regulations refer to malignant *and* benign neoplasms and tumors. If a substance meets the other criteria (e.g., testing with positive results in two mammalian species), it is placed into category I even if all tumors formed are benign.

REGULATION OF CONSUMER PRODUCT SAFETY

The Consumer Product Safety Commission (CPSC) administers two laws that are applicable to carcinogenic substances, the Consumer Product Safety Act (CPS Act) and the Federal Hazardous Substances Act (FHS Act).

The FHS Act speaks of toxicity and health hazards and the CPS Act of "risk of death, personal injury, or serious or frequent illness," but neither speaks of carcinogenicity. The CPS Act is concerned with substances ("products") used by consumers—in the home, for recreation, etc. The prime intent of the FHS Act is to cover household substances. Foods, drugs, cosmetics, tobacco, pesticides, and many types of radiation are excluded from the jurisdiction of both Acts.

Carcinogens that fall under the coverage of either Act can be banned, restricted, or required to be properly labeled. Such actions arise from the "toxicity" of carcinogenic substances. The CPS Act explicitly requires balancing frequency and severity of risk against the effects of regulatory actions on cost, utility, and availability of the product. The FHS Act does not include provisions for taking into account the benefits (or the "costs" of regulating—for example, economic impact), but in making rulings under this Act the Commission takes such considerations into account to a limited extent.

The Commission has not developed its own procedures for identifying and classifying carcinogens. It relies primarily on other organizations for information. The National Cancer Institute and the National Academy of Sciences are its two prime sources.

One interesting quirk of the statutes could pose some problems for the Commission's regulation of carcinogens. Seventeen years ago, when the FHS Act was signed into law, there was much less concern about regulating carcinogenic substances. The FHS Act contains explicit guidelines for the type of animal testing that is considered sufficient to ban or restrict a substance, but only for *acute* toxicity. There are no guidelines for chronic toxicity testing and thus no mention of or guidance for testing of carcinogens. This gap has led critics to argue, according to the CPSC, that the authority of the Commission as defined by the FHS Act is very weak in the area of regulating carcinogens.

LAWS OF THE ENVIRONMENTAL PROTECTION AGENCY

The Environmental Protection Agency (EPA) administers eight separate statutes; five of these have provisions that relate to the identification and regulation of environmental carcinogens. Four of these statutes are concerned with specific environmental areas: Clean Air; Clean Water; Safe Drinking Water; and Insecticides, Fungicides, and Rodenticides ("pesticides"). The fifth, the Toxic Substances Control Act, is an umbrella statute designed to cover gaps in the regulatory coverage of environmental carcinogens (and other toxic substances).

None of the EPA statutes establishes regulatory criteria or actions to be taken when a substance is identified as a carcinogen as opposed to its identification as a toxic substance in general. Thus, in general, carcinogens are regulated in the same manner as other pollutants.

There is no Delaney-type clause in any of these statutes, although an argument could be made that a type of "partial-Delaney clause" exists in single sections of two of the Acts (see below). The Administrator of EPA must weigh the risks to health from exposure to a carcinogen against the costs of controlling its use and the benefits of allowing continued use. The use of such a benefit-risk analysis permits EPA to take into account technological feasibility (e.g., technical ability of an industry to remove the carcinogen from its waste products or final products), economic impact, and ability to enforce or monitor regulatory standards effectively. The EPA can set discharge or emission levels (exposure limits) at zero for a known carcinogen, but it is not required to do so.

A possible exception to the above statement is contained in section 307 of the Federal Water Pollution Control Act and in section 112 of the Clean Air Act. These sections relate to substances that have been identified as definitely hazardous to the public health. The Environmental Protection Agency is required to establish emissions standards for substances so identified and covered by the appropriate act. Some people have viewed these sections as "partial-Delaney clauses." Although EPA is not required to set zero-exposure levels, at the same time it is not specifically directed or allowed to apply benefit-risk analysis. The only criterion identified is hazard to health. Thus, once a substance is identified as a carcinogen (or otherwise very dangerous), the immediate and serious public health hazard would be eliminated by setting a zero exposure limit.

Despite the general lack of specific references to carcinogenicity in the EPA statutes, the EPA Administrator takes this risk into account as a matter of policy. That is, the benefits of allowing the carcinogenic product to be used must be great enough

to offset the greater health hazard posed by a carcinogenic substance. Thus, the "cutoff" point in the benefit/risk weighing is shifted to favor public health and becomes more conservative because of the serious long-range health danger of carcinogens.

CASE STUDY: THE "BANNING OF TRIS"

Contrary to popular belief, the chemical "tris" has not been banned entirely. The Consumer Product Safety Commission (CPSC) has banned only tris intended for use in children's apparel. Although many of the circumstances surrounding tris and saccharin are similar, the cases contrast. A description of the tris case highlights an important difference in the regulatory authorities of the two agencies involved, FDA and CPSC.

The chemical tris was used in children's apparel, especially sleepwear, in order to meet safety standards for flame retardation issued by the CPSC under the authority of the Flammable Fabrics Act. As with saccharin, some indication of the carcinogenicity of tris existed for some time prior to the decision to ban, but CPSC did not consider it convincing. In March 1976, the Environmental Defense Fund (EDF) petitioned the CPSC for a review of the health danger of tris. The EDF did not believe that there was enough evidence of carcinogenicity to ban tris at that time, but requested that CPSC require labeling of tris-treated apparel that would indicate the potential health risk. Several months after the petition was received, CPSC announced it would await the results of a National Cancer Institute rodent-feeding study before making any decision. The results were made available in February 1977, and CPSC decided that the positive findings of those tests, combined with the other evidence available, provided sufficient reason for banning tris-treated children's apparel. The ban took effect on April 8, 1977. Tris-treated adult apparel was not banned because: (1) several of the specific pieces of evidence (for example, the rate of ingestion when children suck on garments) apply only to children, and (2) since no safety standard requires flame retardant adult apparel, then tris or other flame retarding chemicals are rarely used in that apparel.

In deciding to institute the ban, CPSC did consider the economic impact of the ban, the availability of alternate chemicals (there are some), and the benefits of the use of tris-as well as the overall risks to health from its use. This balancing contrasts to the banning of saccharin, where none of the above factors are allowed to enter the analysis. The demonstrated carcinogenicity of saccharin was the only allowable factor in the decision by FDA. Thus, the regulatory discretion of CPSC in this matter was greater than that of FDA in the case of saccharin.

On June 23, 1977, the district court of South Carolina overturned the ban on tris for procedural reasons. The ruling is being appealed and does not affect the present use of the ban as an example of regulatory discretion,