DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 170, 184, 186, and 570

[Docket No. 97N–0103]

Substances Generally Recognized as Safe

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to clarify the criteria for exempting the use of a substance in human food or in animal feed from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because such use is generally recognized as safe (GRAS). FDA is also proposing to replace the current GRAS affirmation process with a notification procedure whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. Under the proposed notification procedure, the agency intends to evaluate whether the submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. This proposal reflects FDA's commitment to achieving the goals for the Reinventing Food Regulations part of the President's National Performance Review (hereinafter referred to as Reinventing Food Regulations). The proposed notification procedure would allow FDA to direct its resources to questions about GRAS status that are a priority with respect to public health protection.

DATES: Written comments by July 16, 1997, except that comments regarding information collection should be submitted by May 19, 1997. The agency proposes that any final rule that may issue based on this proposal become effective 60 days after its date of publication.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington,

FOR FURTHER INFORMATION CONTACT:

Regarding Human Food Issues: Linda S. Kahl, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3101.

Regarding Animal Feed Issues: George Graber, Center for Veterinary Medicine (HFV–220), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1731.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

A. The 1958 Amendment

In 1958, in response to public concern about the increased use of chemicals in foods and food processing and with the support of the food industry, Congress enacted the Food Additives Amendment (the 1958 amendment) to the act. The basic thrust of the 1958 amendment was to require that, before a new additive could be used in food, its producer demonstrate the safety of the additive to FDA. The 1958 amendment defined the terms ''food additive'' (section 201(s) of the act (21 U.S.C. 321(s))) and ''unsafe food additive'' (section 409(a) of the act (21 U.S.C. 348(a))), established a premarket approval process for food additives (section 409(b) through (h)), and amended the food adulteration provisions of the act to deem adulterated any food that is, or bears or contains, any food additive that is unsafe within the meaning of section 409 (section 402(a)(2)(C) of the act (21 U.S.C. 342(a)(2)(C))).

Congress recognized that, under this scheme, the safety of an additive could not be established with absolute certainty, and thus provided for a science-based safety standard that requires producers of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of an additive (Ref. 1). FDA has incorporated this safety standard into its regulations (§ 170.3(i) (21 CFR 170.3(i))). If FDA finds an additive to be safe, based ordinarily on data submitted by the producer to the agency in a food additive petition (FAP), the agency issues a regulation specifying the conditions under which the additive may be safely used.

In enacting the 1958 amendment, Congress recognized that many substances intentionally added to food would not require a formal premarket review by FDA to assure their safety, either because their safety had been

food or by virtue of the nature of the substances, their customary or projected conditions of use, and the information generally available to scientists about the substances. Congress thus adopted, in section 201(s) of the act, a two-step definition of ''food additive.'' The first step broadly includes 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 food. The second step, however, excludes from the definition of ''food additive'' substances that are generally recognized, among experts qualified by scientific training and experience to evaluate their safety (''qualified experts''), as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or through experience based on common use in food) to be safe under the conditions of their intended use.

Importantly, under section 201(s) of the act, it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption. In addition, it is well settled that a mere showing that use of a substance is ''safe'' is not sufficient to exempt the substance from the act's definition of ''food additive'' (*United States* v. *An Article of Food * * * Coco Rico, Inc.*, 752 F.2d 11, 15 n. 4 (1st Cir. 1985)). Instead, the substance must be shown to be ''generally recognized'' as safe under the conditions of its intended use (*Id.*; *United States* v. *Articles of Food and Drug * * * Coli-Trol 80*, 518 F.2d 743, 745 (5th Cir. 1975)). The proponent of the exemption has the burden of proving that the use of the substance is ''generally recognized'' as safe (*Id*). To establish such recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance. (See *United States* v. *Western Serum Co., Inc.*, 666 F.2d 335, 338 (9th Cir. 1982); *United States* v. *Articles of Drug * * * Promise Toothpaste*, 624 F.Supp. 776, 778 (N.D. Ill. 1985), *aff'd* 826 F.2d 564 (7th Cir. 1987); *United States* v. *Articles of Drug * * * Hormonin*, 498 F.Supp.2d 424, 435 (D.N.J. 1980).) Unanimity among experts regarding safety of a substance is not required. (See *United States* v. *Articles of Drug * * * 5,906 boxes*, 745 F.2d 105, 119 n. 22 (1st Cir. 1984); *United States* v. *An Article of Drug * * * 4,680 Pails*, 725 F.2d 976, 990 (5th Cir. 1984); *Coli-Trol 80*, *supra*, 518 F.2d at 746; *Promise* [illegible] However, the existence of a severe conflict among experts regarding the safety of the use of a substance precludes a finding of general recognition (*4,680 Pails*, *supra*, 725 F.2d at 990; *Premo Pharmaceutical Laboratories* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980)) (*Cf. Coli-Trol 80*, *supra*, 518 F.2d at 746 (mere conflict among experts is not enough to preclude a finding of general recognition)).

It is on the basis of the GRAS exemption to the food additive definition that many substances (such as vinegar, vegetable oil, baking powder, and many salts, spices, flavors, gums, and preservatives) are lawfully marketed today without a food additive regulation. Under the 1958 amendment, a substance that is GRAS for a particular use may be marketed for that use without agency review and approval. However, when a use of a substance does not qualify for the GRAS exemption or other exemptions provided under section 201(s) of the act, that use of the substance is a food additive use subject to the premarket approval mandated by the act. In such circumstances, the agency can take enforcement action to stop distribution of the food substance and foods containing it on the grounds that such foods are or contain an unlawful food additive.

Importantly, under section 201(s) of the act, the GRAS exemption applies to the premarket approval requirements for food additives only. There is no corresponding exemption to the premarket approval requirements for color additives, which are defined in section 201(t) of the act.

B. History of FDA's Approach to the GRAS Exemption

1. The GRAS List

Shortly after passage of the 1958 amendment, FDA clarified the regulatory status of a multitude of food substances that were used in food prior to 1958 and amended its regulations to include a list of food substances that, when used for the purposes indicated and in accordance with current good manufacturing practice, are GRAS. This list was incorporated into the agency's regulations as § 121.101(d) (now parts 182 and 582 (21 CFR parts 182 and 582)) (24 FR 9368, November 20, 1959). As part of that rulemaking, however, FDA acknowledged that it would be impracticable to list all substances that are GRAS for their intended use (formerly § 121.101(a); current § 182.1(a)).

Section 121.101(d) became commonly [illegible] added other categories of substances (e.g., spices, seasonings, and flavorings) to the GRAS list in subsequent rulemakings (25 FR 404, January 19, 1960; and 26 FR 3991, May 9, 1961).

2. Opinion Letters

Many substances that were considered GRAS by the food industry were not included in the agency's GRAS list. Under the 1958 amendment, a substance that is GRAS for a particular use may be marketed for that use without agency review and approval. Nonetheless, as a practical matter, manufacturers who determined on their own initiative that use of a substance qualified for the GRAS exemption frequently decided to obtain the agency's opinion on whether their determination was justified. Many manufacturers wrote to FDA and requested an ''opinion letter,'' in which agency officials would render an informal opinion on the GRAS status of use of a substance. Although convenient and expedient, these opinion letters were often available only to the requestor. Moreover, these opinion letters were not binding on the agency at the time they were issued and were in fact formally revoked in 1970 (21 CFR 170.6, 35 FR 5810, April 9, 1970).

3. Agency-Initiated GRAS Review

In 1969 (34 FR 17063, October 21, 1969), FDA removed various cyclamate salts, a family of nonnutritive sweeteners, from the GRAS list because they were implicated in the formation of bladder tumors in rats (Ref. 2). In response to the concerns raised by the new information on cyclamates, then-President Nixon directed FDA to reexamine the safety of GRAS substances (Ref. 3), and FDA announced that the agency was conducting a comprehensive study of substances presumed to be GRAS (35 FR 18623, December 8, 1970). The purpose of the study was to evaluate, by contemporary standards, the available safety information regarding substances presumed to be GRAS and to issue each item in a new (i.e., affirmed) GRAS list, a food additive regulation, or an interim food additive regulation pending completion of additional studies.

4. GRAS Criteria and the GRAS Affirmation Process

In the notice announcing the comprehensive agency review of presumed GRAS substances, FDA proposed criteria that could be used to establish whether these substances should be listed as GRAS, become the subject of a food additive regulation, or [illegible]

regulation pending completion of additional studies (35 FR 18623). These criteria were incorporated into the agency's regulations as § 121.3 (precursor of current § 170.30 (21 CFR 170.30)) (36 FR 12093, June 25, 1971).

FDA made a second announcement that it was conducting a study of presumed GRAS substances (36 FR 20546, October 23, 1971) and subsequently instituted a rulemaking to establish procedures that the agency could use, on its own initiative, to affirm the GRAS status of substances that were the subject of that review and were found to satisfy the criteria established in § 121.3 (proposed rule, 37 FR 6207, March 25, 1972; final rule, 37 FR 25705, December 2, 1972). These procedures were subsequently codified at § 170.35 (a) and (b) (21 CFR 170.35 (a) and (b)). Because the GRAS review did not cover all GRAS substances (e.g., it did not cover many substances that were marketed based on a manufacturer's independent GRAS determination), that rulemaking included a mechanism (the current GRAS petition process; § 170.35(c)) whereby an individual could petition FDA to review the GRAS status of substances not being considered as part of the agency's GRAS review.

In 1974, the agency proposed to clarify the criteria for GRAS status, the differences between GRAS status and food additive status, and the procedures being used to conduct the current review of food substances (39 FR 34194, September 23, 1974). The final regulations based on this proposal amended § 121.3 (current § 170.30) to distinguish a determination of GRAS status through scientific procedures (scientific procedures GRAS determination; current § 170.30(b)) from a determination of GRAS status through experience based on common use in food (common use GRAS determination; current § 170.30(c)) (41 FR 53600, December 7, 1976). Those final regulations also established definitions for ''common use in food'' (current § 170.3(f)) and ''scientific procedures'' (current § 170.3(h)). FDA subsequently added criteria (§ 170.30(c)(2)) for the determination of GRAS status through experience based on common use in food when that use occurred exclusively or primarily outside of the United States (53 FR 16544, May 10, 1988).

5. The Plant Policy Statement

FDA's ''Statement of Policy: Foods Derived From New Plant Varieties'' (the plant policy statement) (57 FR 22984, May 29, 1992) is an example of a recent agency policy announcement regarding [illegible] GRAS status of substances added to food. In the plant policy statement, FDA reviewed its position on the applicability of the food additive definition and section 409 of the act to foods derived from new plant varieties in light of the intended changes in the composition of foods that might result from the newer techniques of genetic modification such as recombinant deoxyribonucleic acid (rDNA) techniques:

> The statutory definition of ''food additive'' makes clear that it is the intended or expected introduction of a substance into food that makes the substance potentially subject to food additive regulation. Thus, in the case of foods derived from new plant varieties, it is the transferred genetic material and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS.

(57 FR 22984 at 22990)

In the plant policy statement, FDA provided extensive guidance, including criteria and analytical steps that producers could follow, on situations in which producers should consult with FDA to determine whether an FAP is appropriate. FDA also stated its intent to use its food additive authority in regulating foods and their byproducts derived from new plant varieties to the extent necessary to protect public health.

C. Elements of the GRAS Standard

Under section 201(s) of the act, a substance is exempt from the definition of food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts. Accordingly, a determination that a particular use of a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted. In contrast, a determination that a food additive is safe requires only technical evidence of safety.[1] Thus, a GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety. To emphasize this distinction between a GRAS substance and a food additive, and to simplify discussion about the standard for general recognition of safety, in this document, FDA uses the term ''technical element'' when discussing technical evidence of safety and ''common knowledge element'' when discussing general knowledge and acceptance of safety.

The technical element of the GRAS standard requires that information about the substance establish that the intended use of the substance is safe. As discussed in section I.A of this document, FDA has defined ''safe'' (§ 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. Current § 170.30(b) provides that general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive. Similarly, current § 170.30(c)(1) provides that general recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation and must be based solely on food use of the substance prior to that date. Current § 170.3(f) defines ''common use in food'' as a substantial history of consumption for food use by a significant number of consumers.

The common knowledge element of the GRAS standard includes two facets: (1) The data and information relied on to establish the technical element must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. Neither facet is, by itself, sufficient to satisfy the common knowledge element of the GRAS standard.

The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. However, mechanisms to establish the basis for concluding that there is expert consensus about the safety of a substance are more varied. In some cases, publication in a peer-reviewed scientific journal of data (such as toxicity studies) on a test substance has been used to establish expert consensus in addition to general availability. In other cases, such publication of data [illegible]

[1] In issuing a food additive regulation, the agency considers technical evidence of safety but does not address the GRAS standard of general recognition. Thus, in most cases, the agency's issuance of a food additive regulation means that FDA did not consider the possible GRAS status of that substance. In a few cases (e.g., 21 CFR 173.357, cellulose triacetate used as a fixing agent in the immobilization of lactase enzyme preparation), FDA concluded, in evaluating the GRAS status of a substance, that the safety of a use of a substance was not generally recognized and authorized its use as a food additive rather than affirm it as GRAS (59

scientific literature has been supplemented by: (1) Publication of data and information in the secondary scientific literature, such as scientific review articles, textbooks, and compendia; (2) documentation of the opinion of an ''expert panel'' that is specifically convened for this purpose; or (3) the opinion or recommendation of an authoritative body such as the National Academy of Sciences (NAS) or the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) on a broad or specific issue that is related to a GRAS determination.

In this document, FDA is using the term ''consensus'' in discussing the common knowledge element of the GRAS standard. Such consensus does not require unanimity among qualified experts (*5,906 boxes, supra,* 745 F.2d at 119 n. 22; United *4,680 Pails, supra,* 725 F.2d at 990; *Coli-Trol 80, supra,* 518 F.2d at 746; *Promise Toothpaste, supra,* 624 F.Supp. at 782). For example, FDA would evaluate a single published report questioning the safety of use of a substance in food in the context of all the publicly available and corroborative information rather than conclude that such a report automatically disqualifies the substance from satisfying the GRAS standard (*Cf. Coli-Trol 80, supra,* 518 F.2d at 746).

D. The GRAS Petition Process

The rulemaking process in § 170.35(c) whereby manufacturers may petition FDA to affirm that a substance is GRAS under certain conditions of use was designed as a voluntary administrative process whose purpose was to provide a mechanism for official recognition of lawfully made GRAS determinations. To the extent that a person elected to submit a GRAS petition, the process could facilitate an awareness, by the agency as well as the domestic and international food industry, of independent GRAS determinations. However, GRAS affirmation involves the resource-intensive rulemaking process, including: (1) Publishing a filing notice in the **Federal Register**; (2) requesting comment on the petitioned request; (3) conducting a comprehensive review of the petition's data and information and comments received to the filing notice to determine whether the evidence establishes that the petitioned use of the substance is GRAS; (4) drafting a detailed explanation of why the use is GRAS (as opposed to simply being safe); and (5) publishing that explanation in the **Federal Register**. FDA believes that, in practice, this resource-intensive process deters many [illegible] affirm their independent GRAS determinations.

II. Scope of the Proposed Regulations

Based on its experience applying the provisions of § 170.30, FDA is proposing to clarify when use of a substance is exempt from the act's premarket approval requirements because such use is GRAS. In proposing these changes, FDA is: (1) Emphasizing that a GRAS substance is distinguished from a food additive by the common knowledge about the safety of the substance for its intended use rather than by what the substance is, or on the basis of the types of data and information that are necessary to establish its safety; (2) identifying the types of technical evidence of safety that could form the basis of a GRAS determination; and (3) clarifying the role of publication in satisfying the general recognition standard. For consistency with the proposed changes to § 170.30, FDA is also proposing to amend the definition in § 170.3(h) of ''scientific procedures.''

In addition, in keeping with the Reinventing Food Regulations, FDA is proposing to replace the current GRAS affirmation petition process (§ 170.35(c)) with a notification procedure (proposed § 170.36) whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. The submitted notice would include a ''GRAS exemption claim'' that would provide specific information about a GRAS determination in a consistent format. This GRAS exemption claim would include a succinct description of the ''notified substance'' (i.e., the substance that is the subject of the notice), the applicable conditions of use, and the basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food) and would be dated and signed by the notifier. The GRAS exemption claim also would include a statement that the information supporting the GRAS determination was available for FDA review and copying or would be sent to FDA upon request. In addition to the GRAS exemption claim, the notice would include detailed information about the identity and properties of the notified substance and a detailed discussion of the basis for the notifier's GRAS determination.

Under the proposed notification procedure, the agency intends to evaluate whether the notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance [illegible] the notice, FDA would respond to the notifier in writing and could advise the notifier that the agency has identified a problem with the notice. Although information in a notice would be publicly available consistent with the Freedom of Information Act (FOIA), FDA would make readily accessible to the public the notice's GRAS exemption claim, as well as the agency's response to the notice. However, FDA does not intend to conduct its own detailed evaluation of the data that the notifier relies on to support a determination that a use of a substance is GRAS or to affirm that a substance is GRAS for its intended use.

FDA has tentatively concluded that the proposed notification procedure has advantages over the current petition process because the resource-intensive rulemaking that is associated with a petition would be eliminated. This streamlining would allow FDA to redirect its resources to questions about GRAS status that are a priority with respect to public health protection. In addition, the proposed notice is simpler than a GRAS affirmation petition and therefore conceivably would provide an incentive for manufacturers to inform FDA of their GRAS determinations. This would result in increased agency awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances. FDA has also tentatively concluded that the public health would be better served if some resources that are currently directed to the GRAS petition process were redirected to the preparation of documents that would provide the industry with guidance on certain food safety issues for complex substances (e.g., macroingredients or biological polymers, such as proteins, carbohydrates, and fats and oils). Finally, the reduction in resources devoted to the evaluation of GRAS substances would allow FDA to shift resources to its statutorily mandated task of reviewing food and color additive petitions.

In light of its experience in reviewing GRAS petitions, FDA believes that the substitution of the proposed notification procedure for the current GRAS petition process would not adversely affect the public health because the agency would be replacing one voluntary administrative process with a different voluntary administrative procedure that would utilize FDA's resources more effectively and efficiently. Under both the current and the proposed procedures, a manufacturer may market a substance that the manufacturer determines is GRAS without informing [illegible]

informed, while the agency is reviewing that information. Thus, from a legal and regulatory perspective, this substitution is neutral.

FDA is also proposing to remove § 170.30(f), which expresses the agency's intent to review the GRAS status of certain food substances, because § 170.30(f) is redundant with the provisions of § 170.35 (a) and (b) that the agency may, on its own initiative, affirm the GRAS status of substances that directly or indirectly become components of food (§ 170.35(a)) or publish a notice announcing its conclusion that there is a lack of convincing evidence that the substance is GRAS and that it should be considered a food additive (§ 170.35(b)).

FDA's regulations regarding the eligibility of substances used in animal food or feeds for classification as GRAS, and the procedures for affirmation of GRAS status for such substances, are codified at §§ 570.30 and 570.35 (21 CFR 570.30 and 570.35), respectively. FDA is proposing the following: (1) To amend the provisions of § 570.30 that are parallel to the provisions of current § 170.30 (i.e., § 570.30 (a) and (b)); (2) to eliminate the GRAS affirmation petition process provided for in § 570.35 (a) and (c); and (3) to provide the option of a GRAS notification procedure for animal food or feeds that would be parallel to proposed § 170.36. FDA is proposing these changes because the regulations in part 570 (21 CFR part 570) implement the same statutory provisions as the regulations in part 170 (21 CFR part 170).

Finally, FDA is proposing to make certain conforming amendments to §§ 170.38, 184.1, 186.1, and 570.38.

As FDA gains experience with the questions raised by industry in preparing notices, FDA expects, from time to time, to prepare guidance documents on issues of particular interest. However, such guidance documents are not a subject of this proposal.

III. Proposed Revisions to § 170.30—Eligibility for Classification as GRAS

A. General Criteria

FDA is proposing to expand the description of the general criteria provided in current § 170.30(a) for a GRAS determination. FDA is not proposing any changes to the first two sentences of current § 170.30(a), which reflect the language of the GRAS exemption as set out in section 201(s) of the act.

The final sentence of current § 170.30(a) provides that general

be common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. FDA is proposing to amend this provision to define what that common knowledge is (i.e., that there is reasonable certainty that the substance is not harmful under the intended conditions of use). In other words, proposed § 170.30(a) would clarify that the safety standard for a GRAS substance is identical to the safety standard in § 170.3(i) and that a GRAS substance is neither more safe nor less safe than an approved food additive. Rather, the distinction between a GRAS substance and an approved food additive is that, for a GRAS substance, there is common knowledge of safety within the expert community.

B. Scientific Procedures GRAS Determination

1. Establishing General Recognition of Safety

Current § 170.30(b) describes the technical element of a scientific procedures GRAS determination (i.e., that it requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive). Current § 170.30(b) also describes the common knowledge element of a scientific procedures GRAS determination (i.e., that it ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information).

FDA is proposing two changes to the description of the common knowledge element in current § 170.30(b). First, FDA is proposing to broaden this description to clarify the types of technical evidence of safety (currently described only as ''studies'') that could form the basis of a GRAS determination. FDA is proposing this change because the quantity and quality of scientific evidence required to obtain approval of a substance as a food additive vary considerably depending upon the estimated dietary exposure to the substance and the chemical, physical, and physiological properties of the substance; there can likewise be a comparable variation in the scientific evidence that forms the basis of a GRAS determination. Second, FDA is proposing to amend this description to clarify the role of publication in satisfying the common knowledge element. FDA is proposing this change because publication is ordinarily required, but may not always be

knowledge element of the GRAS standard.

Specifically, FDA is proposing to revise § 170.30(b) to provide that general recognition of safety through scientific procedures be based upon generally available and accepted scientific data, information, methods, or principles, which ordinarily are published. Thus, under proposed § 170.30(b), ''studies'' would be one of several types of scientific ''data and information'' that could support the technical element of a scientific procedures GRAS determination. However, depending on the circumstances, other scientific data and scientific information such as that relating to chemical identity or characteristic properties of a substance, as well as methods of manufacture, could support, and in some cases be sufficient to satisfy that element.

In addition, under this proposed revision of § 170.30(b), generally available and accepted scientific principles could be applied to, and relied on as part of, the technical element of a scientific procedures GRAS determination. *Webster's New World Dictionary of the American Language* defines a ''principle'' as ''a fundamental truth, law, doctrine or motivating force upon which others are based.'' For example, the common scientific principle ''the dose makes the poison,'' underlies a determination that a substance is safe for use in food at certain levels even if it exhibits toxicity when present at higher levels. A related scientific principle is that the toxicity of a substance may vary between animal species. FDA relies on both of these scientific principles when determining whether the proposed use of a substance added to food is safe within the meaning of section 409 of the act.

For consistency with this proposed amendment, FDA is also proposing to amend the current definition of ''scientific procedures'' in § 170.3(h). Under the current definition, scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance. FDA is proposing to amend § 170.3(h) by broadening it so that scientific procedures would include scientific data (such as human, animal, analytical, and other scientific studies), information, methods, or principles, whether published or unpublished, appropriate to establish the safety of a substance. In both this proposed definition and the proposed amendment to § 170.30(b), the descriptor

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