

Chapter II

Agency Review of Toxicology Information in Petitions for Direct Food Additives and Color Additives Used in Food

A. Introduction

The food additive petition review process came into existence in 1958 when Congress enacted the Food Additives Amendment¹ to the Federal Food, Drug, and Cosmetic Act (the Act).² This Amendment provides a pre-market safety evaluation process for new substances added to food, "food additives." A similar statute, the Color Additive Amendments of 1960,^{3,4} created analogous requirements for color additives used in foods, drugs, cosmetics, or medical devices. "Color additive" used in food is defined in section 201(t) of the Act; "food additive" is defined in section 201(s) of the Act.

Since 1958, before a food additive may be used, an authorizing regulation must be in effect. Approval of a petition for an additive and issuance of an authorizing regulation require that the Agency conclude that the additive is safe for its intended conditions of use. This safety requirement, embodied in section 409(c)(3)(A), is often referred to as the general safety clause for food additives. When the proponent of the proposed use of the additive has shown that the additive is safe for its intended use, the Agency publishes a regulation in the *Federal Register* establishing permitted conditions for the use of the additive.

When a petition for a direct food additive or color additive used in food is submitted to the Agency, or when the petitioner first contacts FDA, a Consumer Safety Officer (CSO) generally is assigned to the petition. One of the CSO's tasks is to coordinate FDA's review of the petition. When appropriate, the CSO can arrange for the petitioner to meet with other individuals in the Agency to discuss specific issues or problems that arise during review of the petition. All communication with the Agency concerning the status or review of the petition should be made through the assigned CSO. General information about the petition review process has been published;⁵ specific questions should be addressed to the CSO assigned to the petition.

The Act and the Code of Federal Regulations⁶ specify the basic elements that a petition must contain. One of these elements is safety data on the additive, which is usually provided in the form of toxicity studies. Toxicologists, pathologists, and mathematicians evaluate any toxicity studies included in the petition. If appropriate, toxicologists can recommend that carcinogenicity studies be evaluated by special CFSAN committees: the Cancer Assessment Committee (CAC) and the Quantitative Risk Assessment Committee (QRAC); for more information on these committees, see **Chapter II C 5 i and ii**.

Review of toxicity studies and other toxicology information results in an estimate of the acceptable daily intake (ADI) for the direct food additive or color additive used in food. The ADI is typically based on the dose level of the additive in animal studies that was shown to cause no adverse effect, multiplied an appropriate safety factor (often 1/100; see Section 201(s) of the Act⁷). Chronic ingestion of the additive at the ADI is considered consistent with a reasonable certainty of no harm.

FDA urges individuals or corporations preparing to submit petitions for direct food additives or color additives used in food to consult with the Agency early in the planning stages. For example, before the petition is submitted, petitioners can submit toxicity study protocols to FDA for review by Agency scientists. This can help the petitioner perform toxicity studies and prepare data in a form that will expedite the Agency's review of the information in the petition (for more information on expediting review, see **Chapter II B**).

This document delineates the toxicology information deemed appropriate for assessing the safety of direct food additives and color additives used in food. However, guidelines contained in this document are only one possible approach among many to providing the toxicological basis for an assessment of safety. We urge petitioners to discuss alternative approaches and toxicity test protocols with the Agency before toxicity tests are begun.

II B. Expediting Review of Toxicology Information

The Agency recommends that petitioners use the following approaches to minimize requests for additional data and to expedite review of direct food additive and color additive petitions:

- ☐ Make sure that petitions are formatted properly and contain complete and adequate information before submitting them for review. Guidelines and recommendations contained in this publication should be consulted before the petition is submitted.
- ☐ Initiate interactions between petitioner's representatives and Agency CSOs and scientists before the petition is submitted. Such interactions can involve Agency review of toxicity study protocols and Agency recommendations about the extent of toxicity testing that may be recommended to adequately assess the safety of the food additive or color additive used in food.
- ☐ Submit toxicology data in machine-readable form. During review of the safety of a food additive or color additive used in food, it may be necessary for scientific reviewers to re-analyze some of the data in a submission. A large proportion of the work in such a re-analysis is computer entry and verification of data. Therefore, much time would be saved if data are submitted in a machine-readable form (magnetic tape for the IBM mainframe standard or floppy disks for IBM personal computers. Please note that the Agency no longer has the capability to read punched cards). General guidelines for submitting machine-readable data follow, but petitioners are urged to contact the Agency before submitting machine-readable data to discuss modifications to these guidelines.
- ☐ Enclosed with the machine-readable data should be:
 - i) the name of a contact person;
 - ii) a printout of the first 100 to 200 records; and
 - iii) the layout of the data. This would include the location of each variable in the record, the type of variable (*e.g.* character, integer), the permissible range of values, and information about how missing data are stored.
- ☐ Magnetic tape format needs to be 9-track, with 6250 bpi preferred (although 800 and 1600 bpi are also readable). Data should be recorded in IBM-EBCDIC or ASCII, or should be in IBM-TSO or statistical package datasets; please consult with the Agency statisticians about appropriate datasets. Interior labels should be IBM standard with volume number and dataset names. Unlabeled tapes should be accompanied by the record format, record length, blocking factor, and the name of the program that created the tape.
- ☐ Floppy disks should be submitted in duplicate; these should be copy-protected because accidental erasure and destruction of disks can occur. The data should be submitted in a form readable by software programs to which the Agency has access; please consult with Agency statisticians about acceptable software.

II C. Evaluating Toxicology Information

1. Introduction

Toxicity testing requirements for assessing the safety of food and color additives used in food have evolved over the past years as knowledge in the field of toxicology has expanded. While short-term or acute studies were considered adequate even for major food additives several decades ago, today's recommendations generally include comprehensive, long-term toxicity studies. CFSAN toxicologists exercise their best scientific judgement in determining what toxicity studies are needed for the Agency to adequately assess the safety of a direct food additive or color additive used in food. In making these decisions, the toxicologists take into account what is already known about the properties of a compound, its intended conditions of use, and current standards for toxicity testing.

From data submitted by the petitioner in support of the safety of a direct food additive or color additive used in food, Agency toxicologists determine the no-observed-effect level (NOEL), select an appropriate safety factor, and calculate the acceptable daily intake (ADI) for the substance. These steps are briefly summarized below.

2. No-Observed-Effect Level (NOEL)

Non-treatment-related variations in the incidence of toxic endpoints occur and may depend on a number of factors, including the source of the animals, sex, genetic variations, diet, age at death, environmental conditions and the histological criteria used by pathologists.

However, Agency scientists determine the most sensitive treatment-related toxic endpoint (adverse effect) from the data submitted in support of the petition. This endpoint is the adverse or toxic effect that occurs in test animals at the lowest exposure to the test substance. The highest exposure that does not produce this adverse effect is called the no-observed-effect level (NOEL) or the no-observed-adverse-effect level (NOAEL).

3. Safety Factors

Use of safety factors is based on the observation that toxic substances usually have thresholds below which toxic effects cannot be detected. The safety factor attempts to account for differences between animals and humans and differences in sensitivity among humans. Use of the safety factor is intended to provide an adequate margin of safety for consumers.

For non-cancer endpoints, the NOEL is divided by a safety factor to obtain an estimate of the maximum acceptable daily intake (ADI) of the additive for humans. The selection of a safety factor is based on the biological significance of the endpoint, uncertainties inherent in extrapolating information about adverse effects from toxicity studies in animals to human populations, and other judgmental factors. The food additive procedural regulations (21 CFR 170.22) state that a safety factor of 100 will be used as a general rule in applying animal test data to man. However, exceptions to a safety factor of 100 are permitted in accordance with the nature and extent of data available and the circumstances of use of the food additive. For example, safety factors may be modified because of potentially sensitive sub-populations such as children, geriatrics, individuals with deficiency states, and lack of developed enzyme metabolic systems.

II C 4. Acceptable Daily Intake (ADI)

The acceptable daily intake (ADI) is generally estimated by dividing the no-observed-effect level (NOEL) of a test substance by the safety factor. The NOEL may be expressed as mg test substance per kg body weight of the test animal or as percent or ppm (parts per million) of the test diet for the animal. The ADI is usually expressed in mg additive per kg body weight of humans. A food additive generally is considered safe for its intended use if the estimated daily intake (EDI) of the additive is less than, or approximates, the ADI. Because the ADI is calculated to protect against the most sensitive adverse effect, it also protects against other adverse effects occurring at higher exposures to the ingredient.

5. Carcinogenic Risk Assessment

FDA has found risk assessment to be useful for estimating the risk from carcinogenic contaminants of food or color additives used in food, for helping the Agency to set priorities, and for determining the urgency of a regulatory action.⁷

Under the general safety clause of the Act, FDA has used risk assessment procedures to determine the upper limit of risk to the consumer from the presence of a carcinogenic contaminant or constituent chemical. For example, FDA approved for permanent listing D&C Green No. 6, which had not been shown to be a carcinogen in appropriate tests, even though it contains the carcinogenic impurity, *para*-toluidine. In this decision, FDA stated its belief that the lifetime upper limit of risk could adequately be estimated from animal data and extrapolated to humans. Although FDA continues to be concerned about carcinogenic contaminants in the food supply, the Agency believes that this approach can be used, where appropriate, without compromising FDA's mandate to protect the public health.

a. CFSAN's Cancer Assessment Committee (CAC)

The Cancer Assessment Committee (CAC) is comprised of CFSAN experts in such fields as pathology, toxicology, mathematics, food chemistry and technology, epidemiology, and nutrition. These experts are charged with ensuring a uniform and consistent scientific approach for dealing with diverse problems of carcinogenicity throughout the broad regulatory purview of CFSAN. The CAC reviews all lifetime feeding studies submitted to the Agency in support of the safety of direct food additives and color additives used in food. The risk assessment process also can be triggered when a newly petitioned or previously regulated food or color additive presents a question of possible carcinogenicity. If the CAC determines that a substance is a carcinogen, and if it is believed that a quantitative risk assessment may have impact on the regulation of the substance, the CAC informs the Quantitative Risk Assessment Committee (QRAC, see **Chapter II C 5 b**) of this decision.

Figure 1 is a flow chart depicting in schematic fashion the groups involved in the risk assessment process at CFSAN. **Figure 2** identifies the steps involved in risk assessment at CFSAN; each of the steps in **Figure 2** is associated with a particular group or set of groups in **Figure 1**.

Figure 1

Flow Chart Depicting the Various Groups Involved in the Assessment of Cancer Risk at the Center for Food Safety and Applied Nutrition (CFSAN) of the Food and Drug Administration

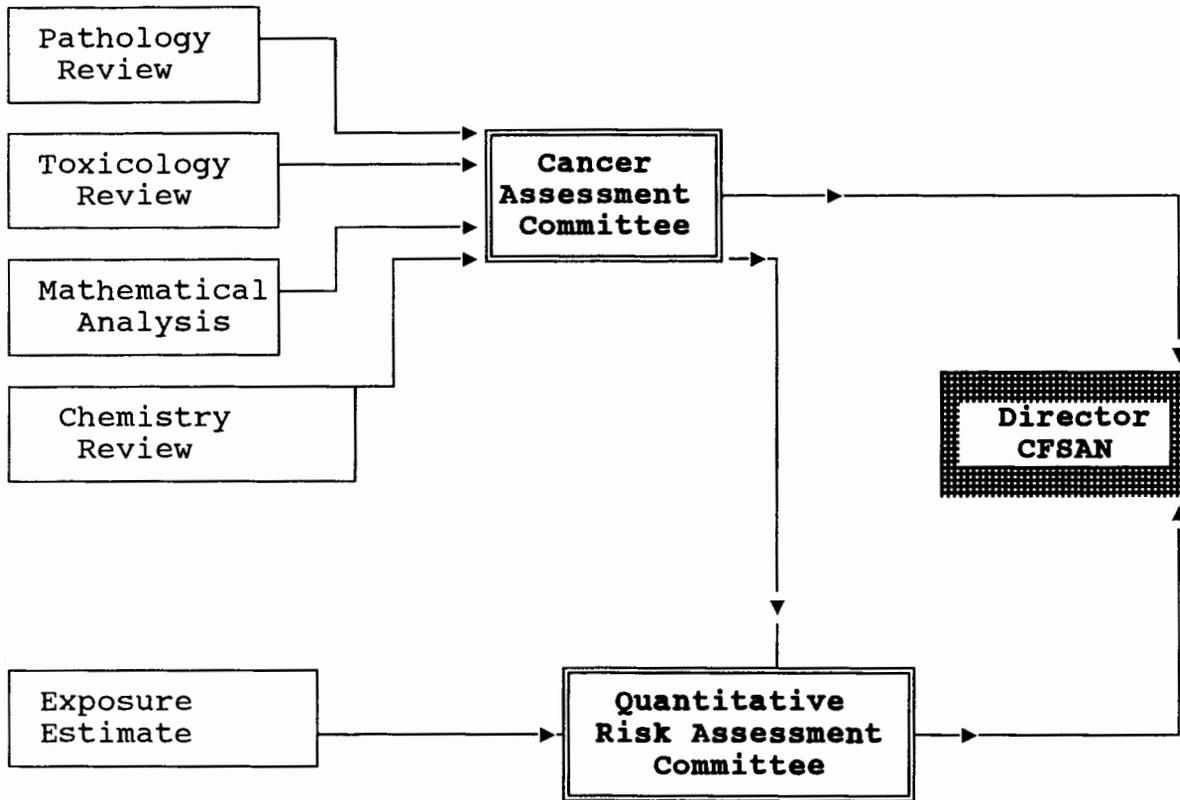


Figure 2

Four Steps in the Risk Assessment of Additives in Food at FDA's Center for Food Safety and Applied Nutrition

1. Toxicological Evaluation

- **Input Obtained from Internal Experts**
 - Toxicologists
 - Chemists
 - Other Experts
 - Pathologists
 - Biostatisticians
 - Epidemiologists
- **Input Obtained from External Experts** (where need is indicated)

2. Cancer Assessment Committee (CAC) Evaluation

- **CAC Reviews input from Internal and External Experts**
 - Is the Substance a Likely Carcinogen?
If Yes: CAC recommends the studies, tissue sites, species, and sex suitable for quantitative risk evaluation if risk assessment is allowed under the statute
If No: No further consideration by CAC or QRAC is needed

3. Quantitative Risk Assessment Committee (QRAC) Evaluation

- **QRAC Reviews Data and Exposure Potential**
- **QRAC Chooses Risk Assessment Model and Procedure**
- **QRAC Estimates Magnitude of Potential Human Risk**
 - Calculate the Upper Bound Lifetime Risk

4. Action Taken by Director of CFSAN, FDA

- **Makes Risk Management and Policy Recommendations to the Commissioner**

II C 5. Carcinogenic Risk Assessment Continued

As indicated in **Figure 1**, the CAC plays a central role in the risk assessment process at CFSAN. This standing committee, which was established in 1978, is made up of 10 CFSAN individuals with expertise in the various scientific disciplines related to chemical carcinogenesis: pathology, toxicology, mathematics, and food chemistry and epidemiology. The decisions of the CAC with respect to issues of science are authoritative and invariably form the basis for CFSAN's recommendations to the Commissioner.

In addition to reviewing information presented by the disciplines indicated in **Figure 1**, the CAC may request additional information from internal and external experts, such as a review of available epidemiological data or a special review of mutagenicity data. The CAC may choose to postpone a final decision on the carcinogenicity of a compound pending the outcome of ongoing or anticipated animal or analytical experiments. In some cases, the CAC may request that CFSAN pathologists review microscope slides from an animal bioassay. External scientific peer review is sometimes requested by the CAC when a particularly difficult or controversial scientific issue is involved.

In general, FDA and CFSAN follow the National Research Council guidelines for risk assessment, described in *Risk Assessment in the Federal Government: Managing the Process*.⁸ FDA and CFSAN also follow the set of principles for risk assessment contained in the 1985 Office of Science and Technology Policy document, "*Chemical Carcinogens; A Review of the Science and its Associated Principles*".^{9,10}

There are no universally agreed upon ways of evaluating carcinogenicity data. It is necessary that there be interaction between pathologist, toxicologist and statistician. The role of the pathologist is to decide whether an observed lesion is cancerous or noncancerous.¹¹ The role of the toxicologist is to determine whether the lesion is related to the treatment. The statistician's role is to analyze the mathematical probability of occurrence of the tumors by chance or as a result of treatment.

Some suggested approaches to the assessment of the evidence of carcinogenicity of a substance are discussed in the following sections.

- i) Evaluation of the Adequacy of the Design and Conduct of the Bioassay: The first step in the analysis is a general review of the adequacy of design and conduct of the bioassay to decide whether it is acceptable for evaluation and for deriving conclusions about safety. For example: Was the test chemical properly identified and characterized? Were an adequate number of animals of each sex used per group? Was the test chemical administered for the major part of the life span of the animals? Did sufficient numbers of animals in each group survive long enough for possible late-developing tumors to be manifested? Were there unforeseen events, such as an outbreak of infectious disease, that might invalidate the bioassay? Did the bioassay utilize adequate matched control animals for statistical comparison? Were detailed pathological examinations performed for every tissue?

- ii) Evaluation of the Possible Increase in Tumor Incidence: Since it is generally believed that cancers arise independently in various parts of the body, it has become customary to treat each potential target site (*e.g.*, brain, lung, liver, kidney, urinary bladder) separately for evaluation. One general exception is the evaluation of types of tumors that may be multicentric in origin, including leukemia and, possibly, tumors originating in blood vessels or nerves, such as hemangioendotheliomas or neurofibrosarcomas. In general, tumor incidence is defined as the number of tumor-bearing animals having tumors at a specific organ site divided by the total number of animals with that organ examined histopathologically.

II C 5. Carcinogenic Risk Assessment Continued

Judgment of an experienced pathologist is important for proper diagnosing and grouping of lesions for statistical analysis to determine whether or not observed increases in tumor incidence implicate a compound as a carcinogen. The grouping of tumors for statistical evaluation should be based on commonality of histogenic origin. Because it is frequently a matter of arbitrary definition and expert pathologists may disagree about how to designate tumors on the borderline of the continuum between benign and malignant, and because of practical difficulties in categorizing certain tumors as benign or malignant, it is usually necessary to combine the incidence of certain benign tumors with that of malignant tumors occurring in the same tissue and organ for statistical evaluation.

Having recorded the tumors present for each animal, the statistical analysis can be undertaken to evaluate the internal consistency of the data, the reproducibility of the test results, the level of statistical significance, the increase in tumor incidence, the evidence for dose-response relationship or shortened latency period, *etc.* Methods of statistical analysis for carcinogenicity are available.^{12,13,14}

iii) Evaluation of the Extent of Evidence for Carcinogenicity: Because the power of carcinogenesis bioassays that use groups of a few dozen animals is relatively weak for determining carcinogenic activity, it is not surprising that evidence of carcinogenicity is sometimes difficult to establish from a single bioassay. This is so for several reasons, including problems of histological diagnosis, sensitivity of the bioassay, and variability of the background tumor incidence. For these reasons, other correlative information may be necessary to add to the weight of evidence of carcinogenicity of a chemical. In general, the extent of the evidence for carcinogenicity can be determined by considering the following information:

- ☐ the number of species or strains with an increased tumor incidence;
- ☐ the number of positive studies (with different routes of administration and/or doses), if tested in more than one bioassay;
- ☐ the degrees of tumor response (incidence, site, type, multiplicity, *etc.*);
- ☐ evidence of structure-activity relationship;
- ☐ prevalence of dose-response relationship;
- ☐ the results of short-term tests for genetic toxicity;
- ☐ the presence of preneoplastic lesions; and

- ☐ a reduced latency for tumor development or increase in the severity (malignancy of the neoplasia).

Other information, such as whether there was a shortened survival due to the toxicity of the test substance or whether the chemical is tested at or near the MTD, can also add weight to or confound the evidence of carcinogenicity. Information on dose-dependent or nonlinear kinetics from metabolic and pharmacokinetic studies in experimental animals and humans can supplement the assessment of the potential carcinogenic hazard of the additive to humans.

It should be noted that, although general approaches to animal carcinogenesis bioassays are well accepted by the scientific community, opinions about the design, conduct, and interpretation of such test results are not always in agreement and are often the source of scientific debate. This may be due, in large degree, to our lack of knowledge about the mechanisms of cancer induction and progression. Because the Act prohibits the use of

carcinogenic food and color additives, the interpretation of carcinogenicity test results has enormous potential societal and economic impact. Consequently, proper assessment of carcinogenicity data has become an extremely critical function of CFSAN.

b. CFSAN's Quantitative Risk Assessment Committee (QRAC)

The QRAC was formed in 1983. Although quantitative risk assessments were performed under the auspices of the CAC prior to this, the QRAC was formed because of the need for an increasing number of quantitative risk assessments related to food and color additive petitions. Based on its evaluation of all relevant data on a substance, the CAC recommends to the QRAC the bioassays and epidemiological studies most appropriate for low-dose extrapolation. The CAC also recommends to the QRAC the tissue site(s), species, and sex most suitable for quantitative evaluation.

The QRAC then performs a quantitative risk assessment. This portion of the risk assessment process is often controversial, even among experts. Currently, the QRAC uses a linear-at-low-dose approach, similar to that described by Gaylor and Kodell.¹⁵ The QRAC cannot determine the most probable expected human risk for almost any case because of the uncertainties and sources of error inherent in quantitative risk assessment using high-dose animal data. However, the QRAC believes that, in cases where dose-response data are suitable, it can predict a lifetime upper limit of risk with some degree of confidence.

References

1. Food Additives Amendment, Section 409, Federal Food Drug, and Cosmetic Act (1958)
2. Federal Food Drug, and Cosmetic Act (1958)
3. Committee of Labor and Public Welfare [CLPW] (1988) A legislative history of the Federal Food, Drug, and Cosmetic Act and its amendments. A report submitted by Mr. Hill from the Committee on Labor and Public Welfare entitled "Food Additives Amendment of 1958. U.S. Senate report No. 2422 to accompany H.R. 13254. Vol.14:913-937.
4. Color Additive Amendment, Section 706, Federal Food Drug, and Cosmetic Act (1958)
5. Rulis, A.M. (1990) The Food and Drug Administration's Food Additive Petition Review Process. *Food Drug Cosmetic Law J.* 45:533-544.
6. The Act, Section 409 (b) of the U.S. Code of Federal Regulations, Title 21 (1992)
7. Lorentzen, R.J (1984) FDA procedures for carcinogenic risk assessment. *Fd.Technol.* 38(10):108-111.
8. National Research Council [NRC]. (1983) In, Risk assessment in the federal government: Managing the process. Washington, D.C. National Academy of Sciences [NAS] Press. Washington D.C.
9. Office of Science and Technology (1985) In, Chemical carcinogens; A review of the science and its associated principles.
10. Anonymous. (1986) Chemical carcinogens: A review of the science and its associated principles. A report by the U.S. Interagency Staff Group on Carcinogenesis. *Environ. Health Perspect.* 67:201-282.
11. Dua, P.N. and Jackson, B.A. (1988) Review of pathology data for regulatory purposes. *Toxicol.Path.* 16:443-450.
12. Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parish, S., Peto, J., Richards, S. and Wahrendorf,

- J. (1980) Guidelines for simple sensitive significance tests for carcinogenic effects in long-term animal experiments. In, Long-term and short-term screening assays for carcinogens: A critical appraisal. International Agency for Cancer Research [IARC]. Lyon, France. *Monograph Suppl. 2:311-426*.
13. Bickis, M. and Krewski, D. (1985) Statistical design and analysis of the long-term carcinogenicity bioassay. In, Toxicological risk assessment, Vol. 1, Biological and statistical criteria. (D.B. Clayson, D. Krewski, and I. Munro eds.) CRC Press, Inc. Boca Raton, FL. *pp.125-147*.
 14. McKnight, B. (1988) A guide to the statistical analysis of long-term carcinogenicity assays. *Fund.Appl.Technol. 10:355-364*.
 15. Gaylor, D.W. and Kodell, R.L. (1980) Linear interpolation algorithm for low dose assessment of toxic substances. *J.Environ.Path.Toxicol. 4:305-312*.