

U.S. Food and Drug Administration Perspective of the Inclusion of Effects of Low-level Exposures in Safety and Risk Assessment

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A brief overview is provided of some of the general safety and risk assessment procedures used by the different centers of the U.S. Food and Drug Administration (U.S. FDA) to evaluate low-level exposures. The U.S. FDA protects public health by regulating a wide variety of consumer products including foods, human and animal drugs, biologics, and medical devices under the federal Food, Drug, and Cosmetic Act. The diverse legal and regulatory standards in the act allow for the consideration of benefits for some products (e.g., drugs) but preclude them from others (e.g., food additives). When not precluded by statutory mandates (e.g., Delaney prohibition), the U.S. FDA considers both physiologic adaptive responses and beneficial effects. For the basic safety assessment paradigm as presently used, for example in the premarket approval of food additives, the emphasis is on the identification of adverse effects and no observed adverse effect level(s) (NOAEL). Generally, the NOAEL is divided by safety factors to establish an acceptable exposure level. This safety assessment paradigm does not preclude the consideration of effects whether they are biologically adaptive or beneficial at lower dose levels. The flexibility to consider issues such as mechanisms of action and adaptive and beneficial responses depends on the product under consideration. For carcinogenic contaminants and radiation from medical devices, the U.S. FDA considers the potential cancer risk at low exposure levels. This generally involves downward extrapolation from the observed dose-response range. The consideration of adverse effects of other toxicologic end points (e.g., reproductive, immunologic, neurologic, developmental) associated with low exposure levels is also becoming more of a reality (e.g., endocrine disrupters). The evaluation of the biologic effects of low-level exposures to toxic substances must include whether the effect is adverse or a normal physiologic adaptive response and also determine the resiliency of a physiologic system. The public health mandate of the U.S. FDA includes an active research program at the National Center for Toxicological Research and the other U.S. FDA centers to support the regulatory mission of the U.S. FDA. This includes the development of knowledge bases, predictive strategies, and toxicologic studies to investigate effects at the lower end of the dose-response range. Because of the wide diversity of legal and regulatory standards for various products regulated by the U.S. FDA, agency-wide safety and risk assessment procedures and policies generally do not exist. — *Environ Health Perspect* 106(Suppl 1):391–394 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/391-394gaylor/abstract.html>

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Introduction

Three questions posed regarding how regulatory/public health agencies consider the biologic effects of low-level exposures are as follows. Short answers to these questions are given here; more detailed discussion follows.

First, does the understanding of the mechanisms of toxicity affect how the agency assesses risks from exposures to toxic substances? Yes, unless specifically precluded from doing so by statute, e.g., the Delaney clause (1) of the Food, Drug, and Cosmetic Act (FDCA). In most cases there are no available data to consider.

Second, does an understanding of the mechanisms by which the body adapts (e.g., detoxifies, repairs, etc.) to the effects of exposures to toxic substances affect how the U.S. Food and Drug Administration (U.S. FDA) assesses risks from exposures to toxic substances? Yes, unless specifically precluded from doing so by statute, e.g., the Delaney clause (1).

Third, if low doses of toxic agents induce apparently beneficial responses (e.g., enhanced longevity, lower incidence of disease), how does and/or could the U.S. FDA address this? The U.S. FDA is required by law to consider the efficacy of human and animal drugs, biologics, and medical devices. Benefits, except where specifically excluded by statute (e.g., food additives) are considered. It is generally difficult to weigh risks versus benefits.

A brief overview is provided of some of the general safety and risk assessment procedures used by each of the U.S. FDA centers to evaluate low-level exposures of toxic agents in consumer products. Different centers of the U.S. FDA are responsible for the safety of foods and cosmetics, veterinary drugs, medical devices and radiation, human drugs, and biologics.

Center for Food Safety and Applied Nutrition

The Center for Food Safety and Applied Nutrition (CFSAN) is responsible for ensuring the safety of cosmetics and the food supply in two major areas: food additives and natural and anthropogenic environmental contaminants. The legal and regulatory standards in the federal FDCA (2) that apply to these areas allow for the consideration of benefits for environmental contaminants, but may preclude them from consideration for food additives (e.g., prohibition by the Delaney clause) (1). Even for foodborne contaminants, benefits

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Abbreviations used: CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health; CFSAN, Center for Food Safety and Applied Nutrition; CVM, Center for Veterinary Medicine; FDCA, Food, Drug and Cosmetic Act; NCTR, National Center for Toxicological Research; NOAEL, no observed adverse effect level(s); SAL, sterility assurance level(s); U.S. FDA, U.S. Food and Drug Administration.

may or may not be taken into account if the hazard or risk assessment is confined to the delineation of a safe level of exposure. This depends on which portion of the act serves as the basis for a regulatory action (e.g., Section 402 of the FDCA: may or ordinarily render injurious to health standard). For carcinogenic contaminants in foods, food and color additives, and cosmetics, the CFSAN considers the potential cancer risk at low exposure levels. This involves the downward linear extrapolation from the observed dose-response range (3–5), which is primarily observed in a chronic animal bioassay. When not precluded by statutory mandates, the CFSAN considers other relevant issues such as mechanism of toxicity, biologic or physiologic adaptive responses, and beneficial responses at low exposure levels. The basic safety assessment paradigm as presently used—for example in the premarket approval of food additives—does not include consideration of these issues. The basic safety assessment paradigm generally involves dividing no observed adverse effect level(s) (NOAEL) by safety factors to derive an acceptable exposure level to toxic agents. Indeed, the act that concerns food additives mandates the use of safety factors with appropriate experimental animal data (e.g., a NOAEL). At the same time there are no specific legal or regulatory barriers that would prohibit the consideration of such information. Furthermore, the safety assessment paradigm does not preclude the consideration of the mechanism of toxicity and physiologically adaptive or beneficial effects at low-dose levels. With the current safety assessment paradigm the emphasis is on the identification of adverse effects, the NOAEL, and use of safety (uncertainty) factors based primarily on laboratory animal studies. Presently the safety and risk paradigm does not accommodate low-dose beneficial effects information. Mechanistic information, when available, can be used qualitatively in identifying the appropriate study for selecting the NOAEL. If an acceptable daily intake is derived that falls within the dose range and demonstrates a beneficial or physiologic effect, there is presently no general process in place that allows us to resolve this conflict. Current processes to consider such conflicting information are ad hoc. Invariably, the estimated safe level of exposure drives the decision-making process, and the issues of low-dose beneficial or physiologic effects have little impact. The flexibility to consider these issues depends on the product

under consideration. For example, unlike direct food additives, with foodborne contaminants these issues can be given more consideration and are more likely to have a greater impact on decision making. Consideration of benefits depends on the margin of safety for a contaminant, i.e., the ratio of the acceptable level to the human exposure level. If the differential between the estimated exposure and acceptable or tolerable daily intake for contaminants is great enough, benefits will generally be considered. If the differential is small, consideration of benefits is more problematic and similar to the difficulty described above for food additives. The consideration of adverse effects of some toxicologic end points (e.g., reproductive, immunologic, neurologic, developmental) associated with low exposure levels is also becoming more and more of a reality (e.g., endocrine disrupters). As our ability to measure biologic events at lower exposure levels becomes more sensitive, our commensurate ability to interpret their clinical and health significance must keep pace. The consideration of biologic and physiologic effects of low-level exposures to toxic substances must begin with the determination as to whether the effect is deemed to be adverse or a normal physiologic adaptive response. There is a need to consider the resiliency or reservoir of response of a physiologic system. If exposure to a toxic substance is deemed not to be adverse but it adds to a cumulative insult that diminishes reserve physiologic capacity, then the issue of whether a physiologic effect is adverse must be defined in this context of diminished physiologic capacity.

Center for Veterinary Medicine

The Center for Veterinary Medicine (CVM) evaluates laboratory and clinical data for animal drugs and feed additives for food and nonfood animals. Management of the risk of these products (derived from regulatory risk-assessment decisions for the use of animal drugs and feed additives) include the development of safe concentration values in food, residue tolerances for postmarketing monitoring, and withdrawal periods for slaughter following drug treatment.

The diethylstilbestrol proviso (6,7) of the Delaney clause (1) permits the use of a carcinogenic drug or feed additive for animals under certain conditions. The proviso stipulates that a suspect or known carcinogen can be administered to animals if no residue of the drug or additive is found in edible products for human consumption

by methods prescribed by the U.S. FDA Commissioner. The U.S. FDA, by regulation, has provided that the permitted concentration of a potentially carcinogenic residue corresponds to that concentration that would give a maximum lifetime risk of cancer of 1 in 1 million (the operational definition of no residue). An analytical method sensitive enough to detect chemical residues at this level is then required to provide adequate assurance of safety. This low level must be determined from the results of chronic studies of the veterinary drug. These studies are generally conducted in rodents for 2 years, with the highest dose at or near the maximum tolerated dose to elicit potential carcinogenic and/or chronic health effects. Hence, risks associated with low-level exposures require an extrapolation procedure described previously for foodborne contaminants. A nonthreshold, conservative, linear-at-low-dose extrapolation procedure for tumor incidence is used to provide estimates of an upper limit of low-dose cancer risk (3–5). The justification for this procedure is that it provides an upper bound for dose responses that curve upward in the low-dose region (3,4). For a genotoxic carcinogen that reacts directly with DNA, presumably a single molecule at the right place and time can initiate a carcinogenic process in a cell but few initiated cells progress to cancer. Further, for those ongoing carcinogenic processes that produce tumors in unexposed control animals, a threshold dose for that process, if any, has already been surpassed by endogenous or exogenous factors other than the agent in question. In such a case any small amount of a chemical that augments this ongoing process will result in a small increase in cancer incidence that is approximately linear at low levels of exposure (8). Thus, in the absence of other information, linear extrapolation over the low-dose range is considered prudent (3–5,8). Adoption of the concentration of an animal drug residue in food associated with a conservative estimate of cancer risk of less than 1 per million for lifetime consumption is considered to satisfy the U.S. FDA's responsibility to ensure with reasonable certainty that the public will not be harmed.

Further, chemicals that appear carcinogenic at high doses but not at low doses are currently under review at the CVM. Hence, low-dose linear extrapolation may not be appropriate. For example, at high doses an animal drug may disrupt the homeostatic control and lead to a chronic elevation in the thyroid-stimulating

hormone. This elevation in turn leads to increased thyroid growth and thyroid tumors. Homeostatic control appears to minimize hormonal imbalance at low doses with no additional risk of thyroid tumors. Thus, there appears to be a dose below which thyroid tumors would not be produced or, at most, there might be a negligible increase in tumor incidence. Hence, mechanisms of toxicity that cause adverse effects only under specific conditions of exposure, e.g., high doses, are currently under consideration by the CVM.

Center for Devices and Radiological Health

The Center for Devices and Radiological Health (CDRH) administers the medical device and electronic product radiation control provisions of the federal FDCA. By implementing these provisions the CDRH evaluates risks in the context of a premarket review system that includes balancing risks and benefits.

One issue that arises in the premarket review of devices is material safety. Some medical devices contain chemicals that can leach out into surrounding tissue in potentially toxic amounts. The doses of such leachants are generally small and amenable to risk assessment by classical procedures. For carcinogenic leachants low-dose linear extrapolation techniques can be used for chemical contaminant risk assessment (3-5). Often one of the most challenging problems is the determination of the low levels of exposures to leachants.

The CDRH has used risk-assessment methodologies to estimate the risks associated with radiation-emitting products. For example, assessments have been made for malfunctioning diagnostic and therapeutic X-ray machines to determine if there were any significant risks of genetic, carcinogenic, or reproductive health effects. Skin cancer risks have been estimated by the CDRH for ultraviolet-emitting sunlamps, tungsten halogen lamps, and fluorescent lamps. Risk assessments have also been conducted for the potential adverse health effects produced by exposure to microwave and extremely-low-frequency radiation from products such as cellular telephones and police radar systems and for possible adverse health effects of ultrasound diagnostic imaging systems. Based on the mechanisms and experimental data for ionizing radiation, a linear dose response has been used for estimating the risk of leukemia and a linear-quadratic model for solid tumors. For genetic effects from

ionizing radiation, exposure limits have been set on the assumption that a small addition to background radiation exposure would be tolerable. For example, the television receiver standard has been set as 5% of natural background radiation exposure to the gonads.

The development of adverse health effects after exposure to microbially contaminated products represents a potentially significant public health concern. The CDRH is collaborating with the National Center for Toxicological Research (NCTR) to develop an approach for characterizing the risk posed by exposure to microbially contaminated medical devices. Specifically, this approach is being developed to provide additional scientific bases for sterility assurance level(s) (SAL) established by the CDRH for devices. An SAL is the probability of at least one microorganism, potentially capable of multiplying and producing infections, existing on a device after it has been submitted to a sterilization process.

Center for Drug Evaluation and Research

The mission of the Center for Drug Evaluation and Research (CDER) is to approve drugs for marketing that are safe, effective, and provide benefits that outweigh their risks. Additionally, the CDER helps ensure that product quality and safety are maintained during marketing.

Risk assessment in the drug approval process is unique because assessments of the risks of a drug are conducted based on actual studies of the drug in humans at levels of exposure likely to be encountered by the population using the drug after approval. The level of exposure in clinical trials is determined on the basis of dose-response and dose-ranging studies designed to estimate the effective dose and conducted in both animals and humans. The risks identified during the controlled clinical trials are evaluated for the general population who will be using the drug. If the benefits of drug therapy exceed the risks, the drug will be approved.

Preclinical animal studies are conducted to identify the potential hazards associated with a drug. They provide early approximations of the margin of safety (ratio of toxic dose in animals to the intended human dose) of the drug as well as estimates of efficacy. The primary purpose of animal studies is to identify highly toxic drugs and drugs that are potentially carcinogenic, genotoxic, or reproductive/developmental toxicants. These results are used in the

design of future clinical studies to minimize risks of participants. Concern about toxicity depends on the mode of action, efficacy, and duration of drug use. Traditional low-dose extrapolation is rarely used to evaluate the results of preclinical animal studies for drugs. It may be used, for example, to estimate the risk associated with contaminants in drug products in a manner similar to the low-dose methods described earlier. More commonly, a risk assessment for a drug involves mechanistic data and a weight-of-evidence approach for a qualitative risk/benefit analysis. This approach uses information from preclinical studies and relevant clinical studies to try to determine relevance of the findings for human risk under the proposed conditions of use. The conclusion from such an analysis is then qualitatively factored in with the drug's known clinical characteristics in the approval decision.

Center for Biologics Evaluation and Research

The Center for Biologics Evaluation and Research (CBER) is responsible for protecting and enhancing the public health by ensuring the purity, potency, safety, efficacy, and availability of biologic products. Biologic products include vaccines, antisera, allergenic extracts, blood, blood products, and blood derivatives.

Biologic products for the most part are complex materials, often derived from living materials from living donors capable of transmitting infectious agents. Thus, they must be closely evaluated and monitored during the production process and in postapproval surveillance to ensure the continued safety and efficacy of the product. Evaluations involve review of source and quality of the starting material, purification, reagents, and contaminants, and include validation of removal or test of residual levels in the final product.

Safety concerns relating to biologic products have resulted in the design of studies to assess carcinogenic (including tumorigenic) and noncarcinogenic end points (e.g., infection, aberrant immune responses, immunosuppression, etc.). The diversity of both traditional and novel biologic products has often demanded the use of nontraditional preclinical methods and approaches to assess potential risks. Adventitious agents such as retroviruses and other persistent viral infections may be associated with acute disease with varying incubation periods, which may be followed by a period of clinical latency prior to the onset

of clinically evident malignancies or other chronic disease. The guidance on viral validation is intended to diminish the risk of transmission of infectious agents to the recipient and to the general public.

The techniques used for estimating risks associated with contaminants, excipients, and leachants from devices used to deliver biologic products are similar to the low-dose safety assessment procedures discussed previously.

The CBER approach to risk assessment and risk management decision-making processes for biologic product approval and surveillance is similar to that of the CDER. The availability of controlled human data during the premarketing phase reduces the uncertainty of exposure and thus provides important data not only to assess the predictive value of preclinical animal data but to select the most appropriate animal model(s) to improve the extrapolation of such data.

National Center for Toxicological Research

The NCTR conducts scientific research that supports and anticipates the current and future regulatory needs of the U.S. FDA. This involves fundamental and applied research designed specifically to define biologic mechanisms of action underlying the toxicity of products regulated by the U.S. FDA. This research is aimed at understanding critical biologic events in the expression of toxicity and at developing methods to improve assessment of human exposure, susceptibility, and risk.

Toxicologic research has traditionally sought to understand basic tenets of biologic and biochemical sciences. As toxicology is evolving from a descriptive science to one based on mechanistic understanding, the hope often is expressed that mechanistic information will eventually reduce, and in some cases eliminate, uncertainty in predicting the toxicity of chemical products. Research on mechanisms of action is generally expensive and complex. Mechanistic data on occasion can be used to discount a mode of action, but are seldom adequate to validate a mode of action.

One aspect of the NCTR program is to conduct concept-driven research that addresses longer-range regulatory needs of the U.S. FDA. For example, studies are being conducted using advanced molecular biology on carcinogenic agents that exert their effects through indirect or secondary mechanisms, dietary modulation of toxicity, and foreign body (biomaterial) carcinogenesis research to assess immune response and identify the role of oxidative DNA damage. Measurements of DNA adducts, cellular proliferation, and apoptosis are being considered for improvement of predicting cancer risk. Biologically based pharmacokinetic models are being developed to estimate doses of toxicants to fetuses during pregnancy. Knowledge of receptor mediation or saturable toxification and detoxification influences the choice of dose-response models for predicting toxicity. Gradually our knowledge of mechanisms of toxicity also is improving our ability to estimate benchmark

doses (9) associated with low incidence of adverse events.

In addition to research conducted by the NCTR, a pool of scientists assists other U.S. FDA centers on specific scientific issues.

Summary

Under the federal FDCA the U.S. FDA regulates a diverse array of consumer products including food, drugs, cosmetics, animal drugs, biologics, and medical devices. The legal and regulatory standards permit the consideration of benefits for some products. Both adaptive biologic and beneficial health effects are considered when not precluded by statutes. For end points other than cancer, the emphasis is on the identification of the NOAEL and the use of safety factors to establish acceptable levels of exposure. The consideration of the biologic effects of low-level exposures to toxic substances must determine whether an effect is adverse or a normal adaptive response. For carcinogenic contaminants cancer risk at low exposure levels is generally estimated by linear extrapolation below the experimental dose range.

The U.S. FDA is conducting research on toxicologic effects to develop knowledge bases and predictive strategies for biologic effects at the low end of the dose range corresponding to human exposure levels. Because of the wide diversity of legal and regulatory standards for various consumer products regulated by the U.S. FDA, agency-wide safety and risk assessment procedures and policies generally do not exist.

REFERENCES

1. U.S. Congress. Food Additives Amendment. Public Law No 85-929. Washington:U.S. Government Printing Office, 1958.
2. Federal Food, Drug, and Cosmetic Act. U.S. Code, Title 21. Washington:U.S. Government Printing Office, 1999.
3. Gaylor DW, Kodell RL. Linear interpolation algorithm for low dose risk assessment of toxic substances. *J Environ Pathol Toxicol* 4:305-315 (1980).
4. Lorentzen RJ. FDA procedures for carcinogenic risk assessment. *Food Technol* 38:108-111 (1984).
5. Gaylor DW, Kodell RL, Chen JJ, Springer JA, Lorentzen RJ, Scheuplein RJ. Point estimates of cancer risk at low doses. *Risk Anal* 14:843-850 (1994).
6. U.S. Food and Drug Administration. Sponsored compounds in food-producing animals; criteria and procedures for evaluating the safety of carcinogenic residues. *Fed Reg* 50(211):45530-45556 (1985).
7. U.S. Food and Drug Administration. Sponsored compounds in food-producing animals; criteria and procedures for evaluating the safety of carcinogenic residues; animal drug safety policy. *Fed Reg* 52(251):49572-49590 (1987).
8. Crump KS, Hoel DG, Langley CH, Peto R. Fundamental carcinogenic processes and their implications for low dose risk assessment. *Cancer Res* 36:2973-2979 (1976).
9. Crump KS. A new method for determining allowable daily intakes. *Fundam Appl Toxicol* 4:854-871 (1984).