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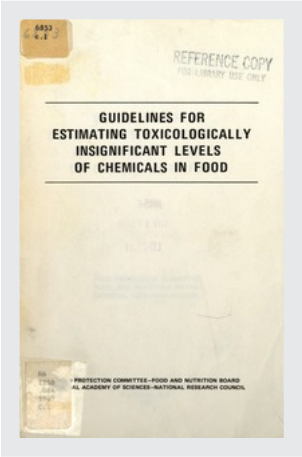

Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food (1969)

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GUIDELINES FOR ESTIMATING TOXICOLOGICALLY INSIGNIFICANT LEVELS OF CHEMICALS IN FOOD

FOOD PROTECTION COMMITTEE
FOOD AND NUTRITION BOARD
NATIONAL RESEARCH COUNCIL

National Academy of Sciences—National Research Council
Washington, D.C.
1969

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PREFACE

This statement was developed for the Food Protection Committee by a special task force to which the Committee expresses its appreciation. The Task Force comprised: H.F. Smyth, Jr., Chairman; J.M. Coon; J.P. Frawley; R.L. Hall; B.L. Oser; A.T. Schramm; and J.A. Zapp. W.J. Darby and Richard Henderson in their respective capacities as chairman of the Food Protection Committee and the Industry Committee of the Liaison Panel served with the Task Force.

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INTRODUCTION

In 1958, the Food Protection Committee issued a statement[1] that pointed out that for every chemical there is some finite level, sometimes called the "safe level."[2] at or below which it can be present in food without prejudicing safety. The safe level of a substance is usually established through extensive toxicological study and expert evaluation. It is generally set by applying some factor, called the "safety factor," to the highest dietary intake that is found not to injure experimental animals exposed under close observation for extended periods. Thus, the safe level is frequently expressed as 1/100 of the experimentally determined "no-adverse-effect level." This ratio, 1:100, provides a conservative estimate of the safety factor needed to afford adequate protection, even to persons whose dietary patterns or individual susceptibilities are unusual. This procedure has been so widely adopted by national and international bodies concerned with food safety that the term "safe level" as applied to chemicals in food is generally understood in the sense set forth here.

Uses of a chemical that in total contribute a level to the diet close to the "safe level" should be regulated to prevent risk to the consumer from avoidable or adventitious excesses. The 1958 statement referred to above recognized that when any particular use results in a dietary level well below the safe level, the possibility of hazard from use or misuse becomes so remote that regulatory activity to protect the public from the chemical in question is superfluous. Such low levels are sufficiently presumptive of safety that they may reasonably be termed "toxicologically insignificant." No attempt was made in 1958 to define "toxicologically insignificant" in quantitative terms. In this statement we now propose guidelines for quantitatively defining levels of chemicals in food that can be administratively considered as toxicologically insignificant.

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[1] "Insignificant Levels of Chemical Additives in Foods". *Food Drug Cosmetic Law Journal*, 13:477-479, 1958.

[2] The "safe level" in the sense here discussed refers to the maximum acceptable daily intake in the total diet. It is not to be equated with "tolerances," which are legally established limits to the concentration of chemicals permitted in agricultural products or foods compatible with good agricultural or manufacturing practice. Tolerances are established with due consideration of safe levels.

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It is axiomatic that no substance should be allowed to enter food unless there is convincing evidence that the amount used will be safe beyond reasonable doubt. This principle is embodied in food regulations (21 CFR 121.1 i) which define safety as the reasonable certainty that no harm will result from the intended use of the food additive.

In the period since the Committee's 1958 statement, a considerable body of new or additional toxicological information has accumulated about many chemicals added to foods, the metabolic processes by which the body deals with them, and their acceptable levels of intake. For administrative and regulatory purposes, the safe level has generally been derived in the manner outlined above as a conservative fraction of the "no-adverse-effect level" found in animal testing. However, if a level in the feeding test that permits survival of at least some of the animals for the duration of the test is found to produce cancer, it may not, according to the Food, Drug, and Cosmetic Law, be used in any concentration in or on food. An observation of any such serious condition makes it prudent to consider the nature of the dose-response relationship and the physiologic, metabolic, or pathologic processes involved to insure against the possibility that the same effect might occur in man.

The vast majority of the chemical entities that we consume are present naturally and unavoidably in foods. Only a small proportion of these substances have so far been identified, and an even smaller proportion have been investigated by conventional toxicological procedures. The levels at which most of them are usually consumed are assumed to be toxicologically insignificant because: 1) they have been consumed by man for generations without apparent harm; 2) they are present in foods at extremely low concentrations; and 3) insofar as is known, they are not related chemically to substances of known high toxicity. Thus, based on these criteria, there is a body of empirical knowledge deemed sufficient on which to base a judgement of the safety of virtually all these substances at the levels found in food. The latter two criteria are equally valid when applied to evaluation of safety for use of synthetic substances.

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THE NEED FOR PRIORITIES

Because of the thousands of natural and synthetic substances present in food at low and intermediate levels, it becomes necessary to establish a reasonable system of priorities for the further study of those substances not yet fully evaluated. To study every chemical to the same extent as those that must be used at close to their safe levels would represent an unjustifiable expenditure of effort not contributing significantly to protection of public health. It is neither practicable nor necessary to undertake experimental toxicological studies of every chemical to which man is exposed; to do so would be to assign equal importance to problems of unequal risk. This would deny the value of experience in assessing probable risk. All environmental exposures must be subjected to scientific evaluation, but not all exposures require experimental toxicological study.

To provide optimum assurance of public safety within the limitations of capabilities available, toxicological facilities for evaluating safety must be concentrated on environmental situations in which there is a reasonable expectation that exposure to chemicals may cause real hazards. The definition of a "toxicologically insignificant" level simply as one well below an established safe level is too indefinite and too limiting to be of practical value, since it requires in every case the establishment of a safe level by experiment. To insist that nothing can be assumed to be safe without direct experimental toxicological evidence implies that safety must be proved experimentally before the proof of safety can be considered unnecessary. This denies the value of establishing criteria for insignificance. Thus, there is urgent need to arrive at more specific guidelines for estimating dietary levels that can be considered toxicologically insignificant.

This report endorses and extends the application of the term "negligible" as employed by a previous committee of the National Academy of Sciences-National Research Council[3], which recommended that uses contributing only a small fraction of the safe dietary level, as previously defined, be ignored administratively. But it is concerned in addition with dietary levels of chemicals for which safe levels have not been determined in the laboratory.

[3]Report of the Pesticide Residues Committee June, 1965. A Report of the National Academy of Sciences-National Research Council to the Food and Drug Administration and the U.S. Department of Agriculture.

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THE APPLICATION OF EXPERIENCE

Our search for increasingly toxic pesticides or antipersonnel agents, for drugs active at low dosages, and for naturally occurring toxins has had the expected result of revealing substances that demonstrate toxicity at lower levels than any substances previously known. Thus, if distinction among probable hazards is ignored, the concept of an insignificant level would drift downward to essentially zero. For the practical reasons outlined above, however, we can not afford to ignore the distinctions, outlined in the following, that increasing experience now permits us to make.

Tabulation and examination of compounds in commercial use that may have deleterious effects at low levels reveal that they fall into four general categories:

1. Certain impurities or contaminants of natural origin;
2. Certain essential nutrients and hormones;
3. Certain heavy metals and their compounds; and
4. Certain organic compounds employed for their biological activity.

In the first category are such substances as aflatoxin, botulinus toxin, and tetrodotoxin, which are toxic at concentrations as low as 0.001 ppm. In categories 2, 3, and 4 are a large number of pesticides, pharmaceuticals, and antipersonnel agents that may have biological activity at levels as low as 0.1 ppm. Aside from these classes of compounds, no commercial compound has been demonstrated to produce toxic reactions below a dietary concentration of 40 ppm.[4]

Obviously, the level that can be considered toxicologically insignificant for one category may not, for that reason, be so considered for another category. The criteria for insignificance will vary for different classes of compounds and may change with further research on compounds within classes. Chemicals that exert significant biological effects and that are useful or unavoidable in food or any

[4] J.P. Frawley, "Scientific Evidence and Common Sense as a Basis for Food-Packaging Regulations". *Fd. Cosmet. Toxicol.*, *5* 293-308, 1967.

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other part of the environment will continue to be subjected to laboratory investigations to establish safe levels, and the experience gained thereby will constantly provide the basis for confirming or modifying the earlier conclusions.

Synthetic organic chemicals that are not manufactured specifically for their biological activity must be sharply distinguished from naturally occurring toxins or trace contaminants. During development and production of a new commerical chemical, some form of toxicological testing is a commonplace precaution. Additionally, a degree of biological knowledge is gained through human exposure in development and production of a new chemical that is more extensive than the knowledge we have of most trace contaminants. It is virtually certain that unpredicted effects of extremely toxic compounds would be revealed through exposure in the work environment, and such compounds would then be placed in category 4 of the above tabulation.

The toxicology of substances intentionally used for their biological activity is always investigated experimentally to establish limits of their safe usage.

ESTIMATION OF TOXICOLOGICALLY INSIGNIFICANT LEVELS

It is generally true that exposure by non-oral routes may not be a reliable basis for predicting a maximum safe dietary level. Nevertheless, unavoidable industrial experience provides useful guidance that can be applied to evaluating safety in the diet, including judgment as to toxicological insignificance for various classes of substances, based on available information concerning their safety or that of related compounds.

Except for the categories of compounds cited under 2, 3, and 4 on page 4, no single organic chemical that has advanced from the laboratory, through development, into general commercial use has been demonstrated to be toxic to experimental animals at a dietary level of 40 ppm or less. Compounds that possess greater toxicity have either been developed specifically for use as economic poisons (as defined by the law), as drugs, or as chemical warfare agents, etc., or were found to possess such biological activity during development and were diverted to these uses.

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A. Chemicals in Commercial Production

If a chemical has been in commercial production for a substantial period, e.g., 5 years or more, without evidence of toxicological hazard incident to its production or use, if it is not a heavy metal or a compound of a heavy metal, and if it is not intended for use because of its biological activity, it is consistent with sound toxicological judgment to conclude that a level of 0.1 ppm of the chemical in the diet of man is toxicologically insignificant.

B. Pesticide Degradation Products

Most degradation products of pesticides are less toxic than the parent material. A few exceptions have been experienced, but even in these cases the toxicity of the degradation products is only slightly greater than that of the parent compound. If the safe level of the pesticide is 1 ppm or above, it appears to be a safe working guideline that dietary levels of degradation products below 0.1 ppm are insignificant and undeserving of laboratory investigation.

C. Organic Chemicals Lacking Toxicological Data, but Meeting Special Structural Restrictions

For many substances that are functionally effective in food at dietary concentrations above 0.1 ppm, but still much below any reasonable judgment as to their maximum safe level, as defined in the introduction, there is need to arrive at estimates of toxicologically insignificant levels. For these substances, it is justifiable to employ accumulated scientific experience, and to recognize their structural analogy to other chemicals whose metabolism or toxicity are known. Reasoning by analogy may be used to arrive at conclusions of toxicological insignificance. If a substance meets *all* the following criteria, it may be presumed to be toxicologically insignificant at a level of 1.0 ppm or less in the human diet.

1. The substance in question is of known structure and purity;
2. It is structurally simple;[5]

[5]Examples that are intended to be illustrative, not limiting, are:
(a) Straight-chain or simply branched aliphatic alcohols, acids, and esters.
(b) Linear polymers of ethylene or ethylene oxide.
(c) Cellulose ethers.
(d) Mononuclear aromatic compounds containing only carbon, hydrogen, and oxygen, and equipped with one or more functional groups that include hydroxyl, aldehyde, and keto.

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3. The structure suggests that the substance will be readily handled through known metabolic pathways; and

4. It is a member of a closely related group of substances that, without known exception, are, or can be presumed to be, low in toxicity.[6]

D. Organic Chemicals with Minimal Toxicological Data and Less Closely Related Structures

In cases nearly, but not precisely, meeting the above criteria, a level of insignificance may be established if:

1. There are available adequate scientific studies that establish safe levels of similar magnitude for at least two analogous substances.

2. The acute or subacute toxicity of the new substance and the analogous substances is of the same nature and degree.

A sound estimate of the safe level of the new substances that meets the two foregoing conditions is the lowest safe level of all the analogous substances that have been studied. If the safe levels for all the structurally analogous substances are essentially identical, 1/10 of the estimated safe level may be taken as a toxicologically insignificant level. In the event of appreciable differences among the safe levels of the analogous substances, the insignificant level should be taken as 1/20 of the estimated safe level.

In conclusion, it is important to protection of public health that responsible and reasonable priorities be established to guide research efforts in toxicology. The principle of toxicological insignificance is a valid concept for separating potential health hazards from predictably safe applications. Guidelines on toxicological insignificance are needed to eliminate wasteful diversion of scientific resources in university, industry, and government laboratories. The levels judged to be insignificant by this Committee are conservatively derived from

[6] "Closely related" shall be understood to mean:
(a) Near members of a homologous series.
(b) Geometric or positional isomers that would not be expected to present serious differences in chemical reactivity or steric effects.
(c) Substances of identical basic structure or differing only by (a) or (b) above, and possessing additional functional groups readily accommodated by known metabolic mechanisms.
(d) Compounds readily metabolized into substances meeting the other criteria here listed.

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accumulated toxicological experience. They are intended to guide and stimulate—not replace—informed professional and administrative judgment. Like all other judgments of toxicologic hazards, they should not be considered infallible against future evidence; and, as with any experimentally derived toxicologic information applied to evaluation of safety for man, continuous awareness of posssible unexpected effects must be maintained. However, in light of today's knowledge, application of these guidelines will protect public health and simultaneously allow greater attention to be devoted to projects of greater potential significance to health.

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