



HERCULES INCORPORATED

MEDICAL DEPARTMENT

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July 12, 1968

Members Ad Hoc Committee on Insignificant Levels

Gentlemen:

At our first meeting I announced that I would take no active part in preparing a draft report for our committee, because I had already expressed my views (within a more limited area) in three separate articles and that I couldn't say it again without it sounding the same.

However, after reading, re-reading and studying the third draft of our report, I was forced to conclude that we are still afraid to face the problem of insignificance with courage. To propose that we cannot consider anything as insignificant, regardless of the level--even 0.000001 ppm--unless the four conditions on page 5 are satisfied, can do nothing but create chaos.

I still find it difficult to express my thoughts differently than in previous attempts. However, I am enclosing a very rough draft of another try at it. I emphasize that it is rough, but rather than edit and polish it, I thought I should send it so you can study it before our meeting on Thursday. I expect some of you to have reservations about my proposals, but please think about them and try to decide whether the risk to public health is significant if they are adopted.

After a perhaps too long introduction, I have proposed that 0.1 ppm in the diet of man be considered insignificant without toxicologic data for commercial chemicals which are not pesticides, pharmaceuticals, heavy metals. I have proposed that degradation products of pesticides contributing to man's diet 10% or less of the safe level of the parent compound be considered insignificant. I have proposed that the National Academy appoint a standing committee to collect information on insignificance and annually report on the advisability of altering the above recommendations. I have tried to emphasize that the relative risk in adopting these proposals is no greater than the risk of establishing a safe level for major environmental contaminants after extensive toxicology.

Members Ad Hoc Committee on
Insignificant Levels

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I apologize for boring you with more reading material, but if we follow along the lines of our previous drafts, we will create more problems than we can even conceive.

Sincerely,

Jack

John P. Frawley, Ph.D.
Chief Toxicologist

JPF:vvh

Enclosure

cc: Dr. Paul Johnson
Dr. William J. Darby



D R A F T
July 10, 1968

Prior to the conduct of any toxicological study, the professional investigator must ask himself the questions: What are the potential advantages to society? Can these potential advantages be determined or achieved by the experimental design? If yes, are the advantages to society worthy of the expenditure of time and money?

Toxicology is not an exact science and its operations are not pure research. All toxicological research and testing is directed toward protection of health, usually of man, from levels of chemicals which would be deleterious in one manner or another. Consequently, any decision to conduct a specific experiment should be motivated by the likelihood of protecting health.

Unfortunately, in the field of toxicology, it is difficult to predict the probability of discovering a health hazard without conducting an experiment. Consequently, most toxicological research is motivated by fear of allowing a health hazard to exist if we do not perform the study.

If fear of the unknown is the ^{principal} ~~only~~ basis for deciding whether toxicological studies are necessary to predict safety of an uninvestigated substance, the only logical conclusion is to require complete testing of every substance. Anything short of complete testing, and retesting as more sensitive procedures are developed, leaves a degree of fear of potential hazard which cannot be dispelled by generalities, logic or informed opinion. Moreover, this fear stirs the public and other segments of society to demand greater assurance than is either possible or justified on the basis of existing knowledge.

Fear is a useful emotion, but uncontrolled fear leads to unreasonable actions and reactions out of proportion to the true risk. In the field of toxicology, this fear must be restrained within the relative risks associated with specific environmental exposures.

Professional toxicologists are trained to evaluate risks and they should have an opportunity to direct their research into the most profitable areas--into areas of greatest potential risk.

Obviously, there is a need for establishing priorities for toxicological research. National policies decide the proportion of the total economy which can be directed toward protection of public health. This expenditure must be balanced against the other needs of society for food, clothing, national defense, etc. In so limiting our effort, we accept some degree of risk, as we do when we limit our effort in each and every other demand on our economy. Priorities should change as the needs of the nation change, and if more national effort is needed in toxicology, this need should be recognized and evaluated with other needs.

However, regardless of the size of the total national effort, professional toxicologists have the responsibility to spend these funds in the most fruitful manner. To devote large amounts of these limited resources on problems of low risk and at the same time to ignore problems of potentially high risk is morally indefensible and nationally intolerable--regardless of the social or legal pressures.

In some areas of toxicology, this situation prevails. It is particularly prevalent in the area of trace environmental contamination, particularly to food. Examples of a few of these trace contaminants include many food packaging migrants, pesticide decomposition products and low volume specialty flavoring compounds. Because of rigid interpretation and administration of

recent legislation, these trace contaminants are being subjected to risk analysis and government regulation far in excess of the relative health hazard which could be associated with them. This narrow view of environmental places the total program in double jeopardy because it health not only wastes national resources, but delays identification of more significant hazards. This concern has been expressed by two previous committees of The National Academy of Sciences, but the tendency of government agencies has been toward even greater attention to these trivia, rather than less. This current committee has been constituted to reexamine the issue of insignificance and suggest appropriate action.

The ^{dictionary} meaning of the term insignificant is ~~generally recognized as~~ lacking in meaning or import. It is essentially synonymous with inconsequential and negligible. In the field of toxicology a philosophy has developed that nothing can be assumed to be safe without experimental evidence, regardless of the dosage. This conclusion leads to the dilemma or contradiction that safety must be proved before a decision can be rendered that proof of safety is unnecessary. It is basically a denial of the principal of insignificance.

Within an imaginary society of unlimited technical manpower and finances, this philosophy is tenable; but in reality it assigns equal importance to problems of unequal risk. It is comparable to assigning as much police enforcement against jaywalking as against homicide, both of which have their own ^{quite} but different risk factors. Priorities within the field of environmental health must be established in relation to the risk to health, and these priorities must be redefined as society and technology change. Some mechanism is needed to identify insignificance, so these problems do not drain off our resources. In other words, insignificance must be defined within its dictionary

sense, as lacking in meaning or import, and at the same time within a scientific sense, as so trivial in risk ^{to environmental health} in relation to other environmental exposures as to be unworthy of scientific investigation. Any attempt to define insignificance as a fraction of an established safe dosage is begging the question, although administratively this concept is also needed. We endorse the concept of negligible, as expressed by a previous Committee of the National Research Council, which recommends that dosages less than 5% of the acceptable daily intake (ADI) be ignored administratively. This committee addresses itself to the question of insignificance⁺ levels of chemicals for which an ADI has not been determined in the laboratory.

The only logical basis for selecting any level of a chemical as insignificant is experience. Traditionally, toxicologists have maintained that we cannot accept any level as insignificant if experience has taught us that other chemicals are harmful to health at that level. Over the years we have identified more and more compounds which are toxic at lower and lower dosages. Consequently, our concept of insignificance has been revised downward to a point approach^{wg} zero.

Tabulation and examination of these compounds which have biological effects at trace levels reveals that they fall into three categories: 1) impurities or contamination of natural origin; 2) heavy metals; and 3) commercial organic compounds synthesized and produced because of their biological activity. In the first category we find such substances as aflatoxin, botulinus toxin, and tetrodotoxin, which have demonstrable toxic effects at dietary concentrations as low as 0.0001ppm. In the second and third category we find a large list of pesticidal and pharmaceutical chemicals, as well as anti-personnel agents which

have biological activity as low as 0.1 ppm. Aside from these three classes of compounds, no commercial compound has been demonstrated to possess toxic properties below a dietary concentration of 40 ppm ().

Obviously, the level which can be considered toxicologically insignificant for one category may not be insignificant for another category. However, great progress can be made by defining insignificance for any one such category. Such a decision does not preclude subsequent definitions of insignificance for the other classes of compounds nor does it terminate research on that one category which might yield confirmatory or conflicting experience (since significant environmental chemicals will be subjected to laboratory investigations to establish a level of safety which will constantly provide ^{experience} ~~insignificance~~ either confirming or denying the conclusions on level of insignificance).

It is worthwhile to consider some of the reasons why synthetic commercial organic chemicals which are not manufactured specifically for their biological activity, appear to be inherently less toxic than the other categories. Firstly, toxins and other trace contaminants whether of natural origin or side reaction products in chemical processes are not manufactured for their own sake in a pure or concentrated form. They are unforeseen and adventitious occurrences and if they had been intentionally synthesized, their biological activity would have been recognized. It is inconceivable in today's technology that a compound as toxic as aflatoxin could be developed and manufactured as a commercial product without sufficient exposure to reveal its extreme activity. In reality, any hazard to health associated with the synthesis and manufacture of an unknown

highly toxic substance is experienced in the laboratory and the work environment. Unpredictable extreme toxicity would be observed in the individuals first exposed and the compound diverted into biological screening or rejected as incompatible with commercial operations.

The fact is that experience has failed to reveal a single organic chemical which has advanced from laboratory, through development, into general commercial use which has demonstrable toxicity to experimental animals at a dietary level of 10 ppm or less. All compounds which possess greater toxicity either have been synthesized for high biologic activity or have been recognized and directed into uses which require higher biological activity, as pesticides or pharmaceuticals. Until experience uncovers evidence to the contrary, it is consistent with the other risks associated with evaluation of health hazards of higher dosages of chemicals to conclude that a level of 0.1 ppm in the diet of man is insignificant for commercial chemicals which are not pesticides, pharmaceuticals or heavy metals.

No such conclusion of insignificance is possible for a pesticidal or pharmaceutical chemical because these can be tailored to achieve extreme levels of toxicity, ~~-Moreover, degradation products of pesticides which may be present on feed-pese~~ as exhibited by antipersonnel agents. However, once the toxicity of the pesticides has been established, we concur that 5% of the ADI should be considered administratively negligible or unworthy of regulatory concern. Moreover, degradation products of pesticides are generally less toxic than the parent material, although a few exceptions have been experienced. In these cases the toxicity of the degradation products have been only slightly more

toxic than the parent compound. In the absence of laboratory studies to confirm the toxicity of such degradation products, it is conservatively within the relative risk concept to consider these insignificant if they are present at no more than 10% of the safe level of the parent compound for man. Higher levels of insignificance will frequently be justifiable if degradation products are identical to mammalian metabolites, or structurally innocent of high suspicion. In such cases, there is no reason to consider levels below 0.1 ppm in the diet of man as significant or worthy of laboratory investigation.

The above recommendations are designed to help administrators and scientists devote their time and funds on problems of potential value to society and not waste our limited resources on predictably unprofitable research. No decision of safety is free of risk in the absolute sense, even after extensive toxicology has been performed. Various safety factors are used to provide assurances not attainable through laboratory measurements.

These recommendations on insignificance ^{incorporate} ~~apply~~ safety factors which reduce the risk to a level equivalent to those employed in other decisions of safety. Since toxicology is constantly benefiting from more fundamental discoveries in related professions, all decisions on safety evaluation must be kept under constant review. As additional knowledge and experience accumulate, these levels of insignificance should be reevaluated.

It is recommended that these values be accepted as insignificant. It is also recommended that the National Research Council appoint a standing Committee on Insignificance whose responsibility it would be to constantly collect evidence from all sources on this subject and report annually whether

changes ~~the~~ the levels which we consider to be insignificant should be made.