Air Products

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2 August 1982

Mr. Bob Barnard
Cleary, Gottlieb, Steen & Hamilton
1250 Connecticut Avenue, N.W.
Washington, D.C. 20036

Dear Bob:

Your letter of 22 July transmitting the most recent paper by R. Wilson, et. al., suggests that a reply may be desirable. I am sending you my thoughts on this paper after my first reading in hopes that these may be useful to whomever prepares that reply.

Very truly yours,

John T. Barr
Manager, Regulatory Response

JTB/sjw

Enclosure

cc: D. Hughes - Procter & Gamble

CLEARY, GOTTLIEB, STEEN & HAMILTON
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August 17, 1982

TO: QUAN. RISK S/C
FROM: AIHC
DATE: AUGUST 24, 1982

MEMORANDUM FOR THE RISK ASSESSMENT SUBCOMMITTEE

I am enclosing a set of calculations by John Barr using the new Wilson correlation between LD_{50} and carcinogenicity.

Dick Molyneaux of Shell called to express concern over the use of the LD_{50} correlation, particularly for regulatory purposes and to urge that AIHC send comments to Wilson.

Robert C. Barnard

Enclosure

cc: M. J. Sloan
Richard Molyneaux

Comments on

Use of Acute Toxicity to Estimate Carcinogenic Risk

Zeise, Wilson, and Crouch
Draft version reviewed July 1982

The first question which must be answered is why this exercise is needed. If there were a direct correlation between toxicity and potency, which there almost certainly is not, then all that would be necessary is an ordering of the acute toxicity values to obtain an ordering of potency. Mathematical manipulation of the toxicity values does not increase the utility or the reliability of the numbers. The known human potency ratings could then be inserted into the ranking, and other values of interest obtained by interpolation. Therefore, the entire exercise appears to be superfluous.

Second, if it is correct that there are no-effect doses for acute toxicity, as the authors states, but none for carcinogenicity, as the authors claim, then there is some dose range in which the toxicity-potency relationship fails. This would be in the lower doses, which are the ones of greatest interest here. This failure of the proposed dependency relationship strikes at the heart of the paper.

Thirdly, the authors respond to inconvenient data by ignoring them. When they find a substance with an LD_{50} below the chronic test dose, they merely seek another toxicity figure. This is unacceptable scientific behavior. Such nonconformities must be addressed and a satisfactory answer determined.

Leaving aside for the moment these problems of logic, there are several basic assumptions in the paper which should be addressed.

1. Everything causes cancer

   Whatever support there is for this claim goes beyond the particular properties of a substance and leads to the proposition that life itself causes cancer. This is true, at least from a philosophical standpoint, but hardly is a basis for a quantitative method.

   This statement is contrary to the stoutest claims of the NCI and others. It also is in contradiction of the facts that many bioassays do not yield positive results at, or above, the MTD. These results are bounded by statistical limits, of course, but that should be understood by mathematicians.

   This brings up another question not addressed by the authors, that of those substances which have no LD_{50}, and which may not have, due to physical limitations. Examples are milk, sand, water, foods, etc. Are they then non-carcinogens? If so, this premise is wrong. If they are, the relationship between potency and toxicity fails again, this time at high doses.

The authors concede (p. 44) that "one or two chemicals fall outside the scheme." That is an inadequate apology for a much larger gap in the method.

2. Mouse equals man (with a factor)

   This has been the subject of a great amount of discussion. Most who support some sort of a relationship do so from a sense of prudence, not dogma. These are examples of where animals do not react as do man, e.g. benzene, arsenic, cigarette smoke, on one side, penicillin, etc. on the other. Quantitative data are available on a few substances, such as vinyl chloride that show several orders of magnitude difference in response.

   This premise might be acceptable for a preliminary qualitative assessment, but not for a supposedly sophisticated quantitative procedure.

3. There is no threshold

   Again, volumes have been written here, but there now is general acceptance of nongenetic routes to tumors. Therefore, there are no-effect doses of substances which may be carcinogens under other circumstances.

4. Risk is proportional to average lifetime dose

   This precept of the linear method ignores mechanism of tumorigenicity, time-to-tumor, and biochemistry. It takes no account of whether the dose is one large amount in the last year of life or several toxic doses or a continual small exposure.

   Further, it can be shown mathematically that second order kinetics (the reaction of two substances) is not linear with concentration, but expotential. It is permissible to use the chord of a curve over a short distance as an approximation of the curve, but this may not be done for extrapolations of several orders of magnitude.

This paper is an extension of a pet theme of Wilson's which he has propounded for several years. Simplicity and prudence are the keywords, and here they have been carried to their ultimate. By coincidence, the tribute to Confeld by Armitage, with a discussion by van Rizen* (Current Topics in Biostats. and Epidemiol., 1982 119-139, March). The sophisticated and sensitive discussion of risk analysis by those authors is in stark contrast to the brash and simplistic approach presented here. The problem has been summarized by Mantel (Risk Analysis 1 (2) 101 (1981)) who said, when discussing the Crouch-Wilson paper, "it suffers from the fact that its proponents are working outside their areas of competence." Efforts to make the procedure simple and all-encompassing have glossed over everything but that which is convenient to the proposal.

* arrived in the same mail

This is a reaffirmation of a generations-old distinction between physicists and physical chemists:

> Physicists make excrutiatingly precise measurements on impure substances; physical chemists make sloppy measurements on excrutiatingly pure substances.

This proposal calls for extensive mathematical manipulation of data of assorted reliability in a relationship which is uncertain at best, and unnecessary for the avowed purpose. The results are both superfluous and irrelevant to the basic problem of identification of potential carcinogens.

The basic fault is total dependence on mathematical manipulation, while ignoring all scientific factors. Many specific criticism could be made on the details of the paper. For example, the formaldehyde calculations (p. 37-38) predict an annual incidence of nasal cancer over 3,300 cases, while the total annual nasapharnyx incidence of 1950-69 was about 400 cases. Thus, it does not seem worthwhile to do so when the underlying premise is in error.

J. T. Barr

JTB/sjw