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January 11, 1980

CINCINNATI, OHIO 45217

Dr. Joe Rodericks
Food & Drug Administration - HFY3
5600 Fishers Lane
Rockville, Maryland 20857

Dear Joe:

This will confirm our phone conversation setting January 29, 1980 as the date for a meeting between members of the American Industrial Health Council (AIHC) and representatives of the Interagency Regulatory Liaison Group (IRLG) to discuss in depth specific scientific issues raised in the IRLG risk assessment document entitled, "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks", that appeared in the Federal Register of July 6, 1979. You have kindly consented to hold the meeting at the FDA's Rockville building in Conference Room F beginning at 9:00 a.m.

As we agreed, the objective of the meeting is twofold: first, to illustrate, by focusing on a limited number of specific examples, some of the problems we encounter in attempting to utilize the IRLG document in its present form; and second, to determine if the IRLG representatives have any questions of clarification or on the substance of the AIHC response to their risk assessment document.

The format we agreed on was an in depth discussion of about one hour on each of six compounds and we would initiate the discussion with a 20-25 minute presentation of appropriate data. The proposed agenda is attached. If there are any items you wish to add or modify, please let me know.

We are looking forward to this initial interaction between government and industrial scientists in this area of biology and hope the day's efforts will be both stimulating and productive.

With best regards.

Sincerely,

D. H. Hughes, Ph.D.
Regulatory Services Division

DHH:es
Attachment

cc: E. R. Wilson
G. H. Scott
E. L. Behrens
K. H. Ferber
R. C. Barnard
R. Reitz
J. T. Barr
V. Ray
F. Hoerger
M. Norvell

AP00012740

AGENDA

COMPOUND	ISSUE ADDRESSED	PRESENTER
1. Chloroform	Use of Pharmacokinetics Data	Richard Reitz - Dow Chemical Company
2. Vinyl Chloride	Extrapolation from Animals to Man	John Barr - Air Products
3. NTA	Maximum Tolerated Dose	Don Hughes - Procter & Gamble Company
4. A drug	1. Animal Models 2. Short-Term Tests	Verne Ray - Pfizer
5. Aflatoxin	Species Differences in Response	Fred Hoerger - Dow Chemical Company Kelly Ferber - Allied Chemical Company
6. DES	Genetic vs. Epigenetic Effects	Mike Norvell - Mobil Oil Company

DHH

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Experience with Risk Assessments in the Regulation of Vinyl Chloride

The regulation of vinyl chloride by the Environmental Protection Agency was a watershed in the evolution of regulatory processes, not only because it was one of the early major cases which helped crystalize the thinking of the Agency and thus formed a basis for present policy, but also because it gave the first examples of a formal effort to quantify the risk encountered by large populations to a potential carcinogen. Many of the procedures and philosophies of the present risk assessment effort have evolved from this early effort. Therefore, it will be useful to examine critically and in detail the development of that document.

There are a number of constructive elements in the risk assessment by Kusmack and McGaughy (1) which was prepared near the end of the rulemaking process. First, the authors give us considerable detail on the rationale which was used, so that we do have a good understanding of the many assumptions and decisions which form the basis for their conclusions. Second, they did utilize two mathematical models for the extrapolation of the rat data to low doses, the linear constrained through zero and the modified Mantell-Bryan log-probit. It is unfortunate that the results of the latter effort was ignored by the Agency, but we do have the ability to compare the results of both calculations. Third, an effort was made to estimate an error range for the results. Again, unfortunately, this exercise was not carried back to the underlying data, so that the stated error range is far too narrow, but it was made clear that this process does not produce an single precise number, a limitation which is not always recognized. Finally, an effort was made to compare the results of the

animal data extrapolation to available human data. This comparison was not totally satisfactory because of the use of highly selected and unrepresentative human studies and the reluctance to conclude that a negative epidemiology study was significant, nevertheless an effort was made to compare the calculated results with real life. We regret that none of these steps is apparent in the risk assessments that are being prepared at this time, nor are they given sufficient weight in the IRLG recommendations.

These authors concluded that there was, by a linear model, a lifetime risk of about 7×10^{-5}/ppm exposure to humans, based on one of the Maltoni rat exposure studies, (2) and confirmed by human worker data. We disagree, and believe that a more realistic risk estimate is three or four orders of magnitude lower. In developing our reasons for this disagreement, we will examine in detail several of the assumptions made by the authors and provide data which support our belief.

1. Rat/Human Equivalency

   An underlying assumption in all such extrapolations is the relationship between the sensitivity of the species toward the agent in question and that of humans. In this case, the assumption was made that rats and humans are equally sensitive. It would have been easy enough to interpolate a human exposure estimate on the Maltoni data plot to obtain a projected human risk. In this case, it would have predicted a fatality of about 7%. The actual figure is much less than 0.1%. The National Academy of Science has estimated that the rat is some 500 times more sensitive to vinyl chloride than is man, a figure much more consistent with the data.

2. Use of the Linear-Through-Zero Model

   The authors found that plotting the chosen animal data in a linear model gave a negative intercept, so it was forced to pass through zero. This

choice was made because it was "prudent" and would give an upper limit of risk, and because of ease of calculation. The insertion of societal judgements into scientific determination is not proper. The need is for the best estimates upon which the regulator can depend for making his subsequent socioeconomic judgements. It often is difficult to decide from the raw data which model is more appropriate, for several models may fit the high dose data equally well, and more data are needed to select the proper model. In this instance, Gehring and coworkers (3) have shown that, after proper biotransformation data have been considered, the log-probit and linear-not-forced-through-zero models bracket the actual human experience, while the linear-through-zero and one hit models greatly overestimate the risk. None of the models were accurate when the biotransformation step was not taken. Unless such additional data are available, there is no scientific basis on which to select one model for use, and all appropriate methods should be presented for evaluation. (4)

3. Disregard of the Time to Tumor

The authors assumed that there was no dose response effect on the latency period, contrary to the data and the statement of the experimenter. (2) They then used this incorrect fact to estimate that humans are more sensitive than rats to vinyl chloride because the latent period is a smaller fraction of the species lifetime. The realization that there is an influence of dose on latency is an important facet of risk assessment, because low doses can often fail to initiate response within a normal lifetime. To ignore this fact leads to an overestimation of the risk.

4. Assumption of an Equal Number of Cancers at Other Sites

The direct estimate of angiosarcoma (the rare marker disease for this substance) from the animal data was doubled to allow for an expectation of

cancer developed at other sites. This assumption was based on their evaluation of both animal and human results, but it is not supported by the data. A comparison was made of total neoplasms to angiosarcomas in the rats to arrive at the factor of two, but no allowance was made for the neoplasms exhibited by the controls, when in fact there was no signficant difference in incidence of cancers at other sites between controls and exposed groups at the lower levels of exposures. Much of the difference at higher levels was due to zymbal gland cancer, an organ unique to rodents and especially sensitive to some chemicals. The human data which were relied upon were from selected, and very small cohorts that were not representative. Subsequent studies (5) have not supported the proposition that vinyl chloride is active at other sites, and to make that assumption ignores the biological concepts of site specifity and of pharmacological causes for carcinogencity.

5. Human Data Were Distorted

As stated above, the human data which were relied upon for confirmation of the animal risk estimate were selected subsets of the exposed cohorts. The attached Table 1 is a reproduction of Table 1 from the risk estimate. The authors chose to use the incidence from their Reference 6, the smallest cohort of any, and one which was specifically selected to study one plant where there was known to be angiosorcoma. The study of their Reference 7 also covered one specific plant where cases were known to exist. The authors did acknowledge that as the case size rose, the incidence fell, but ignored the data. When this incidence, after dividing by 70 to give a lifetime value, approximated the rat lifetime incidence, actual exposures not being considered, the authors reported a confirmation of their estimate. Subsequent studies of even larger cohorts (5) have placed the incidence

at less than one per thousand for the more highly exposed VC workers and at zero for fabricator workers with exposure estimated at about 15 ppm. (6) This use of a nonrepresentative incidence has distorted seriously the credibility and accuracy of the document.

6. Exposures were Estimated Incorrectly.

Further errors were introduced by underestimating the worker exposure used to confirm the animal estimate and overestimating the general population exposure values used in calculating the expected number of cases per year.

a. Worker exposure underestimated

The authors took as a basis for their estimate of 200-500 ppm for worker exposure some limited monitoring data from one company which had been a leader in vinyl chloride health studies and which had established an internal standard of 50 ppm several years ago. This is in contrast to the OSHA standard of 500 ppm which ~~was~~ became effective in the early seventies. There was no standard on vinyl chloride before this, and British employers have estimated that the exposure in their plants at that time was well over 1,000 ppm. There is no reason to believe that conditions were different in this country before 1970, especially when there are press reports of persons "feeling dizzy" and even becoming unconcious. This is especially true for those job assignments which produced the highest rates of angiosarcoma, the reactor cleaners.

b. General population exposure was overestimated.

The authors used an Agency estimate of 5 million persons within a five-mile radius at 17 ppb to calculate the 1-10 cases per year of expected angiosarcoma. This estimate (7) comes from doubling the

industry estimate of vinyl chloride released during processing, and among other assumptions the conservative agency diffusion model, which uses no thermal bouancy for the plume, and an average air speed of 1.1 mph. All of the persons in the five-mile radius were lumped together to calculate the average exposures. When the Agency data on population distribution were used to recalculate exposure based on the most recent Agency monitoring results, the calculated exposure value was less than 1 ppb. (8) No detectable quantities were found outside the three-mile radius by EPA where 62% of the population resided. The Agency has never considered its own VC monitoring data in ~~any of~~ its regulatory decisions. Further, it has assumed that all persons spend 24 hours a day at home, an unlikely prospect.

7. Human Epidemiology was Ignored.

The author concluded that a lifetime exposure to 17 ppb of vinyl chloride would cause six cases of angiosarcoma per year for the five million persons exposed, and thus twelve cases per year of total cancer. They examined the results of a ten-year compilation of 286 national angiosarcoma of cases, and concluded that none of these were relatable to being near a vinyl chloride emittor. (7,8) Thus, instead of the sixty expected cases, they found none. Rather than use this substantial evidence to recalculate an upper limit for risk or to reevaluate the rat data, they concluded that positive statements cannot be made about residence near plants being or not being a risk factor. Human data are the most valuable facts which we can obtain, and must not be ignored whenever creditable studies are available.

We have seen this same lack of simple, realistic testing of the results in other risk assessments. The recent development of water quality

criteria for the 65 priority pollutants included risk assessments for several putative carcinogens, many of which failed the test of practicality. A few of these are listed in Table 2. When the risk calculated by these procedures is multiplied by Agency figures for current ambient water content of the pollutant, the resulting expected cases of cancer are totally out of proportion to that actually seen. Again, the risk assessment process can only lose credibility and utility when some realism is not involved in their preparation.

8. The Study Was Made Too Late.

Finally, this risk assessment was not prepared until much too far along into the regulatory process. The Agency had already determined that it would regulate vinyl chloride and has published a proposed regulation when this document became available. Thus, rather than being a vehicle whereby the Agency made decisions as to the need for a regulation, or through which it determined priorities for allocation of Agency resources, or for determining the degree of control that was required, it became merely another supporting document for the action already underway. Risk assessments have too much power and potential value to society to be assigned such a secondary position.

In summary, we are encouraged at the efforts to bring some quantitative measure of the risk posed by potential hazards. However, there are pitfalls in this complex process which must be avoided. Our examination of this pioneering effort by EPA for vinyl chloride has disclosed several desirable features, but also several problems which we see as inherent in the risk assessments being produced by that Agency today and which are present in the recommendation contained in the IRLG proposal. These include:

- Noncritical acceptance and use of data,
- Intermingling of scientific and social judgment in the process,
- Failure to make simple realistic tests of the results, and
- Application of the results too late in the regulatory process.

Each of these can be a fatal flaw in the value of the final product, but none is a problem which cannot be solved by conscientious or concerned scientists. We hope that we can work with you to make quantitative risk assessments a useful and significant tool in the regulatory process.

J. T. Barr

24 January 1980

Table 1

Liver Angiosarcoma Incidence Among Highly Exposed Workers

Reference	Number of Cases	Number People Surveyed	Incidence ($\times 10^{-3}$)
5	6	1,817	3.3
6	3	151	20*
7	7	270	26
8	6	745	8

*study chosen for use

Table II

Calculated Expected Cancer Cases from Recent EPA Risk Assessments

Substance	Document	Calculated Annual Cancer Cases	Type	Actual Rate
Arsenic	PB-292-420	18-64 million	Skin	300,000*
PAH	PB-297-926	1-3 million	Unspecified	400,000**
Asbestos	PB-297-917	2,000	Peritoneal Mesothelomia	very rare+

*usually ascribed to ultraviolet radiation, and does not occur in the area with high arsenic waters. These are largely never fatal types.

**annual death from all types of cancer, many of which have well-defined causes.

+very rare except in highly exposed occupational environments. See Reference 9.

Bibliography

1. "Quantitative Risk Assessement for Community Exposure to Vinyl Chloride". A.M. Kuzmack and R. E. McGaugney, Environmental Protection Agency, December 5, 1975.

2. Origin of Human Cancer. Hiatt, Watson, and Winsten, eds., Cold Spring Harbor Laboratory 1977. "Vinyl Chloride Carcinogenity: An Experiemntal Model for Carcinogen Studies", C. Maltoni, p. 119.

3. "Risk of Angiosarcoma in workers exposed to Vinyl Chloride Predicted from Studies in Rats". P. J. Gehring, P. A. Watonbe, and C. N. Park. TOX and App. Pharm. 49, 15 (1979).

4. See for example, the discussions in reference 3, and in "From Mouse to Man - or How to Get from the Laboratory to Park Avenue and 57th Street", M. Schniderman, N. M. Mantel, and C. C. Brown, p 237 in "Toxicity of Vinyl Chloride - Polyvinyl chloride", Annal. N.Y. Acad. Sci., 246 (1975), Selikoff and Hammond, eds.

5. "Epidemiological Study of Vinyl Chloride Workers Final Report" (Prepared for the CMA - formerly MCA - Washington, D.C.) by Equitable Environmental health, Inc., Rockville, MD., January, 1978.

6. "Report on a Mortality Study Covering Employees of PVC Fabricators", Organization Resources Counselors, Inc., Washington, DC., February, 1976.

7. "Standard Support and Environmental Impact Statement: Emission Standard for Vinyl Chloride." EPA-4501 2-75-009, October, 1975.

8. For a full discussion, see the submittals of Air Products and Chemicals, Inc., and the Society of the Plastics Industries to EPA on the proposed standard for vinyl chloride, February 23, 1976 in re 40 FR 59532.

9. "Cancer Risk of Asbestos Exposure", I. J. Selikoff, p. 1765 of ref. 2. See footnote b of table 6.

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5. DES	Genetic vs. Epigenetic Effects	Bill McCarville - Monsanto Chemical Company
6. --	Lifetime Feeding Studies	David Salsburg - Pfizer

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1/28/80