The Vinyl Institute
A Division of The Society of The Plastics Industry, Inc.

Roy T. Gottesman
Executive Director

November 2, 1987

TO: The VI Health, Safety and Environment Committee

RE: American Industrial Health Council Discussion Memorandum on Improving the Science Base for Health Assessment

Recently, Dr. Robert Hinderer of BFGoodrich Company sent me a copy of a document developed by the American Industrial Health Council (AIHC) entitled "The Vinyl Chloride Decision: Improving the Science Base for Health Assessment". This was developed by the AIHC Scientific Committee and the first that I was aware of its existence was when I received the attached from Bob Hinderer. It certainly would have been helpful if this group had consulted with your committee, but unfortunately this was not the case.

These documents are being sent to you for your information. If your company is a member of AIHC, I would urge you to ask your representatives to that organization to request that AIHC coordinate such matters with the Vinyl Institute in the future.

Roy T. Gottesman

RTG/pmb
cc: M. Scheck
P. de la Cruz

AMERICAN INDUSTRIAL HEALTH COUNCIL

September 1, 1987

D I S C U S S I O N M E M O R A N D U M

The Vinyl Chloride Decision:
Improving the Science Base for Health Assessment

The recent unanimous en banc decision by the U. S. Court of Appeals in the Vinyl Chloride case[1] brings into sharp focus the importance of accelerating the integration of developments pointing toward an improvement in the scientific basis of risk assessment for chronic health risks. Currently EPA procedures generate an upper bound unit risk estimate which EPA states is not a prediction of "actual risk". Under the Vinyl Chloride decision EPA can no longer consider the modulating factors of cost and technology in setting a safe level of exposure under Section 112 of the Clean Air Act. That decision provides a significant incentive to update procedures so that the regulatory process is based on the soundest scientific prediction of "actual risk".

Last year Administrator Lee Thomas stated the Agency's "intent to seek data and procedure which will allow the issue of 'most likely' or 'best' estimate of risk to be addressed in future risk assessment guidance."[2] The Vinyl Chloride decision characterized the current methods of risk assessment

as reaching decisions on "the rules of arithmetic rather than because of knowledge." The purpose of this letter is to urge updating procedures so that risk estimates more closely approximate what the Administrator described as "the concept of 'actual' risk"(2) by utilizing more of the biological data and reducing reliance in the "rules of arithmetic."

This memorandum will outline some developments which, if incorporated into the risk assessment procedures, will move significantly toward the goal of using "most likely" or "best" estimates of risk. That estimate should be selected as a judgmental more-likely-than-not value from an envelope of values, including upper and lower confidence limits.

The American Industrial Health Council

The members of the American Industrial Health Council (AIHC) represent a broad spectrum of industry including producers of chemicals, metals, petroleum products, pharmaceuticals and consumer products. AIHC does not act as a sponsor or advocate of any product. We are not addressing vinyl chloride or any other specific agent in this memorandum. Rather, AIHC's objective is to utilize industry capabilities with assistance from the academic community to present proposals for the purpose of improving the scientific basis of the analyses the Agency uses in the regulatory process for dealing with chronic health hazards.

Summary

A sound scientific evaluation of all the data is the optimal basis for regulatory decisions on human carcinogenic risk. The science of carcinogenesis is dynamic, but the EPA cancer risk guidelines are static representing Agency procedures at the time the guidelines were drafted. Incorporation of improvements in the procedures will enable the Agency to utilize "most probable" or "most likely" estimates that more closely approximate the concept of "actual risk".

- Evidence Classification. The system for classification of agents on the basis of the strength of the evidence of carcinogenic activity in experimental animals should be modified promptly. The IARC evidence classification system, upon which the EPA plan is based, has recently been reconsidered. The descriptive title for IARC Group 2B (the counterpart of the Agency's Group B-2) has been changed from "probably carcinogenic in humans" to "possibly carcinogenic in humans;" in recognition that it is not the amount of experimental evidence (positive bioassays) but rather its relevance to human risk that is critical. There is good reason for the Agency to follow the IARC precedent as to the descriptive titles of the categories. This change would enable the selection of the risk assessment methodology for Group B-2 to be based on an evaluation of relevance to man rather than routine application of

the "fall back" procedures required under the guidelines. An alternate would be to make the title more accurate by describing the category as animal carcinogens or to create a new category where human relevance is questionable.

° Mechanism. Significant advances in scientific understanding highlight the conclusion that risk evaluation should utilize available data on mechanism of action rather than the assumptions as to mechanism in the "fall back" procedures. Mechanism data are key in identifying a suitable animal surrogate for estimating human risk.

° Assumptions. Significant research programs at NSF and NCTR relating to the validity of risk assessment assumptions are now, or shortly will be, available to the Agency. (Using the Supreme Court's touchstone in the Benzene case, the generic assumptions in the guidelines should be evaluated under the "more likely than not" criterion.) Decision analysis procedures provide a reasonable method for utilizing this criterion. Since the assumptions are multipliers in the risk estimation process, their use should be explicit. More realistic assumptions will lead to more realistic estimates of "actual risk".

° Extrapolation Models. The NAS study of pharmacokinetics, supported by the repeated recommendations of the EPA Science Advisory Board that

the Agency use pharmacokinetic data in risk assessments, provides the basis for the Agency to express a preference for biologically based models for low-dose extrapolation to replace the current model that uses only part of the available biological data. The use of pharmacokinetic data also provides a sounder basis for evaluation and should replace generic cross/route and cross/species factors specified in the current guidelines.

Incorporating these improvements in the EPA risk assessment procedures will be a significant advance toward the objective of using the most meaningful and soundly based scientific estimate of "actual risk". This will also respond to the Court's comment in the Vinyl Chloride case on reliance on "rules of arithmetic rather than an actual knowledge."

DISCUSSION

Risk Assessment Guidelines: A Background

The development of risk assessment procedures for quantitative assessment of chronic health risks, particularly carcinogenic risks, is barely two decades old. Because it was apparent that the science had developed beyond a simplistic yes/no answer, the Agency issued interim guidelines for assessment of human cancer risks in 1976[3]. The National Academy of Sciences' major report on risk assessment in 1983

provided a valuable guide to the process of risk assessment and a common set of terminology[4]. In 1985 the Office of Science and Technology Policy (OSTP) published a major report on the science of carcinogenesis[5]. That report, written by an interagency work group of government scientists (including scientists from EPA) and subject to extensive peer review, set out for the first time a broad set of principles for evaluating substances as carcinogenic agents. The final OSTP report was approved by all the federal regulatory agencies.

In 1984, the Agency began a process of review of its risk assessment guidelines that led to the publication in 1986 of six risk assessment guidelines[6]. The guidelines on cancer risk assessment are critical to the implementation of Section 112 of the Clean Air Act, and our comments are focused on those guidelines.

Developments Toward Risk Assessment Guidance Addressing "Most Likely" or "Best" Estimates of Risk

The Report of the Office of Science and Technology Policy calls for a weight-of-the-evidence evaluation of relevant mechanistic, pharmacokinetic and metabolic data in determining the relevance of experimental data to human risk. The EPA guidelines are intended as a means to that end. It is important to recognize, however, that the science is dynamic but the guidelines are essentially static, representing an Agency operational consensus at the time the guidelines were drafted regarding risk assessment procedures. Although the EPA guidelines reflect an "openness" to new scientific

developments, their main thrust is a set of "fall back" procedures reflecting assumptions or policy choices adopted for reasons of "conservatism" together with procedures that are designed not to underestimate a risk rather than to predict "actual risk".

There are a number of developments that point the way to "update" the guidelines so as to improve the science base of the analysis required under the Vinyl Chloride decision.

1. Reconsideration of Evidence Classification Systems. One of the basic elements of the Agency guidelines is a system for classifying evidence of carcinogenic activity. The EPA system was patterned on that developed by the International Agency for Research on Cancer (IARC) and classifies evidence of carcinogenic activity into five categories, depending on the strength of the evidence: Group A (human evidence), Group B(1) and B(2) (degrees of experimental evidence), and Group C (limited experimental evidence). The EPA system also includes Group D (not classifiable) and Group E (evidence of non-carcinogenicity). Group B(1) and B(2) are both described as "probable human carcinogens" and as a general policy EPA uses the cancer risk assessment guidelines for estimating risk from exposure of the substances classified in the two B subgroups. Group C has the descriptive title "possible human carcinogen" and the decision whether to use the cancer risk assessment methodology is made on a case-by-case basis.

Until this year IARC also used the descriptive title "Probably Carcinogenic in Humans" for both IARC Groups 2A and 2B (which correspond with EPA's Group B-1 and B-2). It was clear that this characterization by IARC was based on a presumption of human risk, not an evaluation, since IARC does not consider potency or mechanism and does not attempt an evaluation of comparative pharmacokinetics. Nor does IARC evaluate human exposure or the relevance to human risk of the route of exposure. IARC describes its evaluation as merely the "first step" in carcinogenic risk assessment.

Principle 8 in the OSTP Report put the "presumption" used by IARC in scientific perspective. Principle 8 states that the presumption "should not foreclose further inquiry into the human relevance of animal carcinogens." (50 Fed. Reg. 10376-10377).

This background is important to understanding the significance of the change by IARC reflected in the revision of the Preamble to the Monograph Series agreed to earlier this year. IARC has left the characterization of Group 2A unchanged but has now changed the characterization of Group 2B and modified the descriptive title from "probably carcinogenic in humans" to "possibly carcinogenic in humans."(7) This change emphasizes the fact that the IARC classification is the "first step" in the evaluation to assess relevance to human risk.

The Agency recently advised the EPA Science Advisory Board of the importance of the change IARC has made in characterizing Group 2B agents as "possibly" human

carcinogens. This is particularly significant since the Agency has regarded the selection of a risk assessment process as depending on whether the characterization was "probable" or "possible." The change by IARC of Group 2B to "possible" creates an inconsistency between IARC and the Agency's classification system that is based on the old IARC characterization. Since the choice of risk assessment methodology by EPA turned on the characterization of Group B(2) (the counterpart of IARC 2B) as "probable" human carcinogens, a re-examination of the EPA classification system is underway.

Earlier this month the EPA Science Advisory Board's Environmental Health Committee and its Halogenated Organics Subcommittee met to discuss the use of pharmacokinetic data and other scientific information in support of the regulatory decision process. We understand that an issue of classification arose where the evidence of carcinogenic activity in experimental animals was clear, but the relevance to humans was questionable. The re-examination of these issues raises questions as to the characterization of a substance that might be classified in Group B on the strength of the experimental evidence of carcinogenic activity, but the relevance of which to human risk is doubtful.

In this situation we believe it would be reasonable for EPA to follow IARC and change the description of Group 2B to "possible human carcinogen". The consequence would be that the choice of risk assessment methodology would then be made

appropriately on a case-by-case evaluation (as is now done for Group C).

AIHC believes the critical point is that the present classification system does not reflect a true weight-of-the-evidence determination of the relevance of experimental data to human risk. The NAS Report [4] contemplates that all of the evidence would be evaluated and a judgmental determination of the relevance to human risk would be the result of the risk characterization step in the risk assessment process. Under the guidelines, evaluation is made in connection with the initial step (hazard evaluation) in the risk assessment process and is reflected only in the classification system. The fact that IARC changed the description of Category 2B and the emergence of problems from the use of the current system that turns on the strength of the experimental evidence of carcinogenic activity rather than relevance to man indicates the shortcomings of the current system and the need for change.

These developments point to the importance of scientific evaluation of relevance to human risk of substances classified in B(2) because of the strength of the experimental evidence of carcinogenic activity. The selection of the appropriate risk assessment procedure should be based on a full evaluation of relevance to human risk rather than routine application of the guideline "fall back" procedures based on an evidence of a carcinogenic activity classification scheme.

2. Mechanism. A key to evaluating carcinogenic risk is an understanding of mechanism. Scientific advances have made clearer that the mechanism(s) of carcinogenesis are more complex than the generic assumptions used in the current guidelines. Thus the evaluation by the Agency of unleaded gasoline and of certain solvents will require consideration of the unusual susceptibility of the male rat kidney to the hydrocarbon. In other cases the evidence shows an association of the formation of bladder stones with urinary tract tumors that are characteristic of certain species or sexes of experimental animals. An FDA Science Panel recently completed a report on the FD&C dye Red 3 that reached the conclusion that the oncogenic activity of the dye was indirect rather than by direct action on the DNA of the target organ[8]. The FDA Report considered what would be the appropriate risk assessment methodology in view of this evidence. Scientific understanding of the genetic differences in susceptibility among individuals and between species will be recognized as increasingly important.

These illustrations of the rapidly increasing scientific understanding of mechanism highlight the conclusion that a sound scientific evaluation of human risk must incorporate data that are available on mechanism(s) in order to derive a "best estimate" of "actual" human risk. These developments emphasize the shortcomings of a classification system that is not based on a determination of relevance of the experimental evidence of carcinogenic activity to human risk.

3. Assumptions. A key part of the current risk assessment procedure is the use of "assumptions" based on science "policy" or opinion. The assumption on mechanism in the guidelines is one example (referred to above). In the current procedure, assumptions are multipliers. The impact of the assumptions can be illustrated by a chart prepared by Dr. Elizabeth Anderson (then Director of Risk Assessment at EPA) used in a workshop at Harvard in 1984. Dr. Anderson's chart (attached) shows that six of the assumptions can have the effect of magnifying the risk estimate by a factor up to 10,000. (The chart refers to reductions that would result from removal since the assumptions are an integral part of the current procedures.)

A National Science Foundation program under the general direction of OSTP (supported by government agencies including EPA) to evaluate the risk assessment assumptions is well underway and can be expected to make important recommendations regarding the assumptions currently used. The National Center for Toxicological Research also has undertaken as part of the FDA Plan of Action a research program on the validity of the assumptions.

We believe that the Vinyl Chloride decision read together with the Supreme Court decision in the Benzene case[9] provide a reasonable criterion for the evaluation and selection of assumptions (policy choices) to be used in risk assessment in a particular case. The Supreme Court described the burden

on the agency to be to show on the basis of the evidence that it was "more likely than not" that there was a significant risk. The "more likely than not" criterion provides a reasonable basis for judging the relevance of a particular assumption (policy choice) in light of the available data.

These developments offer contributions toward improvements in the procedure with the objective of using the best available scientific bases for assessing "actual" risk:

- A substitution of generic assumption(s) by using data to select assumption(s) on the basis of the "more likely than not" criterion;
- An openness to replace assumptions in light of pharmacokinetic, metabolic or mechanistic data that raise issues of relevance to, or magnitude of, human risk.

EPA Science Advisory Board has repeatedly urged that a sensitivity analysis of assumptions be performed. The EPA guidelines now authorize, but do not require, such an analysis. A sound sensitivity analysis will provide the occasion to assess the assumptions under the "more likely than not" criterion. Certainly such an analysis would provide risk management information to the Agency reflecting the impact of the opinions integrated into the risk assessment as assumptions as well as the reasons for selection. Such a process would provide a sounder scientific basis for decisions than a standard use of generic assumptions under the "fall back" approach.

4. Extrapolation models. There are three stages in the current risk assessment process using extrapolation procedures:

- from high experimental doses to the low doses found in the human situation;
- across routes of exposure - e.g. relevance of ingestion data to a human inhalation risk;
- across species.

The current procedure for low-dose extrapolation (linearized multistage model) uses only part of the available biological data - tumor production as a function of dose. There has been significant progress, sponsored in part by EPA, in the development of a biologically based model that would integrate biological data not now used in the linearized multistage modeling procedure. EPA is also a co-sponsor of the major study undertaken by the National Academy of Sciences last year on the incorporation of pharmacokinetic data in the risk assessment procedure.

The SAB has strongly recommended that EPA improve the quality of its risk assessments by using pharmacokinetics. A pre-publication copy of the NAS Report (due for publication in October) was given to the SAB earlier this month in connection with the SAB review of a Draft Health Assessment Document on methylene chloride evaluating pharmacokinetics, mechanism of action and epidemiology.

Proposals for a biologically based model were recently published by Thorslund (formerly at EPA) and Brown (NCI)[10].

Another study of biologically based models by Dr. Robert A. Sielken (Texas A&M) is in press as part of a series on risk assessment[11].

In Volume 6 of the NAS Report "Drinking Water and Health" (sponsored by EPA), the NAS evaluated physiologically based pharmacokinetic models for dose-route extrapolations.

Study is well advanced to replace the numeric linearized multistage model by a biologically based model. Such a model would also replace the generic factors for cross species and dose-route extrapolation by taking advantage of the new data and the latest scientific understanding of mechanism(s), metabolism and pharmacokinetics.

These changes should also eliminate the criticism of "instability" of most likely estimates generated by the linearized multistage model. The "instability" due to the "crossover" points within the computer program from the linear, quadratic and cubic components of the model will be eliminated in the biologically based models.

EPA is close to a decision point on this matter. Substitution of models using more of the biological data would respond to the Vinyl Chloride court's reference to reliance on "the rules of arithmetic rather than because of any actual knowledge."

A Proposed Program

EPA has embraced the concept of weight-of-the-evidence approach to evaluation of human cancer risk. Guidelines are not an end in themselves, but should be regarded as a means to achieve a soundly based estimate that is predictive of "actual" human risk.

The present guidelines are based on a "fall back" set of assumptions and procedures that are designed to develop an upper-bound estimate, not a prediction of "actual risk". Since risk management decisions under Section 112 of the Clean Air Act must now focus on health considerations in determining safe levels without the modulating effect of technological feasibility, it becomes urgent that current procedures be improved so that estimates use the scientific data and understanding to generate risk values that more closely approximate an estimate of "actual" human risk.

At the present time the evaluation of human risk is normally made under the "fall back" procedures in the guidelines. The result is the virtually exclusive use of upper-confidence limit risk values rather than the scientific judgment as to the most probable value or the best estimate of human risk. In addition, the risk estimate is enlarged by the generic assumptions rather than by reliance on scientific knowledge and judgment.

Stimulating the development of, and incorporation of, the newer data and understanding will improve the scientific

adequacy of the risk estimation and will provide more meaningful and realistic estimation of human risk. One result should be a more useful disclosure to the risk manager of the uncertainties involved and the impact of the scientific "policy" choices on the risk estimate. The use of single number unit risk values gives a false sense of precision and conceals the ranges of values that are involved in the process reflecting the uncertainties and policy choices.

It is vital that evaluation of relevance of experimental evidence to human risk be performed. It is not vital that such an evaluation be made at the hazard assessment step in the process or at the risk characterization step, the final stage in the process as identified by the NAS. In either case, all data and results of the prior steps in the process are scientifically integrated to determine relevance to man. The important fact is that the full scientific evaluation be made and the uncertainties described, together with a judgmental evaluation of the most realistic risk estimate. The current inflexible categorization scheme and the "fall back" procedure on the guidelines do not facilitate such an evaluation. Principles 25 through 28 in the OSTP Report are applicable to a full weight-of-the-evidence evaluation including an examination of all the data, not just those data that are used in a particular extrapolation or modeling procedure.

Conclusion

AIHC strongly urges that recent scientific developments provide the basis for an acceleration of the process of updating the EPA guidelines so that regulatory decisions under the Clean Air Act can utilize an improved risk assessment guidance that provides a "best" or "most likely" estimate of risk using the new data and emerging scientific understanding. This will provide a sounder scientific base for implementing the Court's mandate in the Vinyl Chloride case. Science is dynamic but the procedures in the guidelines are static. The objective of basing regulatory decisions on "actual" risk requires an openness to improved procedures to reflect scientific advances.

A realistic, soundly-based estimate of actual human risk is the optimal basis for decision making under Section 112 of the Clean Air Act. Determination of a safe level based on a soundly based "best" estimate of health risk provides a solid scientific foundation for the use of technological feasibility in determining an "ample margin of safety."

We recognize that the data sets being evaluated will not always contain the information necessary to take full advantage of the latest scientific understanding. The Supreme Court's "more likely than not" test will provide a guide for selection of assumptions and the best use of such data as are available. Moreover, incorporation of the improvements in the EPA evaluation procedures will stimulate research. When it

is known that the data will be used, there is a significant incentive to develop the data.

We would welcome the opportunity to discuss this matter.

References

(1) Natural Resources Defense Council, Inc. v. EPA, #85-1150 (D.C. Cir. July 28, 1987).

(2) Letter dated August 22, 1986 to Dr. Wendy L. Gramm, Office of Management and Budget.

(3) U.S. EPA, Health Risk and Economic Impact Assessment of Suspect Carcinogens - Interim Procedures and Guidelines. 41 Fed. Reg. 21402, May 25, 1976.

(4) "Risk Assessment in the Federal Government: Managing the Process", National Academy Press, 1983.

(5) U. S. Office of Science and Technology Policy, "Chemical Carcinogens; A Review of the Science and Its Associated Principles, February 1985." 50 Fed. Reg. 10372, March 14, 1985.

(6) U. S. EPA, Part II, 51 Fed. Reg. 33992-34054, September 24, 1986.

(7) Preamble, Final Draft, January 1987 "IARC Programme on the Evaluation of Carcinogenic Risks to Humans."

(8) U. S. HHS "An Inquiry Into the Mechanism of Carcinogenic Action of FD&C Red No. 3 and Its Significance for Risk Assessment." A Report by the FD&C Peer Review Panel, July 1987.

(9) Industrial Union Dept. v. American Petrol.Inst. 448 U.S. 607 (1980)

(10) Thorslund, T. W., Brown, C. C. and Charnley, G., "Biologically Motivated Cancer Risk Models." Risk Analysis 7:109-119 (1987).

(11) Sielken, R. A., "Incorporating More Science in Cancer Dose-Response Extrapolation." Environmental Science and Technology, in press.

FACTOR	RANGE OF POSSIBLE REDUCTION IN ESTIMATED CANCER RISK
A. WEIGHT vs. SURFACE AREA	2-12
B. MAXIMUM OR AVERAGE LIKELIHOOD vs. UPPER 95% CONFIDENCE	2-3
C. MALIGNANT TUMORS vs. MALIGNANT PLUS BENIGN TUMORS	1-2
D. AVERAGE ANIMAL SENSITIVITY vs. MOST SENSITIVE ANIMAL	2-5
E. PHARMACODYNAMICS vs. EFFECTIVE DOSE	1-6
F. RISKS AT SHORTER THAN EQUILIBRIUM BUILD-UP TIME	2-5
Total	15-10800

Elizabeth L. Anderson, Ph.D.
"Risk Analysis in Environmental Health with Emphasis on Carcinogenesis"
Harvard School of Public Health, September 18-20, 1984