"We are now as a federal government going to have to embrace the public receiving massive amounts of information on chemicals from" the National Toxicology Program, Young said, noting that many of the chemicals will be found to be positive. With people being exposed to these chemicals, agencies are going to ask, "How do the numbers look?" said Young.

"OSTP is petrified with the very thought," added Young, saying there is concern that some agencies have a tendency to "compound conservativeness over conservativeness over conservativeness. . ."

Young noted that the risk assessments were so damaging on dioxin that "we bought out Times Beach." However, expensive epidemiological studies have been unable to come up with a link between exposure and health effects, Young added, saying this does not mean there is no effect "but no tools sensitive enough to detect it."

Asked how consistency in risk assessment can be achieved when the base of information is so diverse, Young said, "We haven't guaranteed our boss we'll come up with a final product," but added that eventually some efforts must be made to standardize risk assessment.

One idea which has been "bounced around," Young said, is the formation of a scientific, not regulatory, agency where risk assessments would be conducted, such as the Agency for Toxic Substances Disease Registry. He acknowledged that such an agency would have to work with the Office of Management and Budget, "which at times seems to make the final decision."

However, Young said, "no matter who does the risk assessment, the politicians will take the final role," noting that unfortunately there are few scientists in high policy level positions and only one Ph.D. currently in Congress, Rep. Ritter.

Asked whether the four-phase program would be concerned with risk assessment or with risk management, Young said the Cabinet Council Working Group on Risk Assessment "wants to see efforts in both risk assessment and risk management."

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1,3-BUTADIENE ON LEADING EDGE OF DEBATE ON EPA RISK ASSESSMENTS

1,3-Butadiene -- for which OTS is approximately seven months overdue in a TSCA Section 4(f) determination -- was shown to be on the leading edge of controversy over EPA risk assessment methods last week as the agency Science Advisory Board's Environmental Health Committee took up two topics which turned out to be related: a draft health assessment document on the substance and "typical wording of some sections of the agency's health assessment documents."

The Chemical Manufacturers Association pointed out in an appearance before the April 10-11 session of the committee that two different parts of EPA are preparing risk assessments of 1,3-butadiene. OTS had been expected to refer the substance to the Occupational Safety and Health Administration, but the referral may have been delayed substantially by Congressional questioning of the TSCA Section 9 actions (See March 13, Page 21).

The OTS designation of 1,3-butadiene as a priority chemical for study under TSCA Section 4(f) -- under which the agency must make a determination within 180 days, extendable another 90 days -- was in Jan., 1984 (See Nov. 30, 1983, Page 2). Multiple carcinogens were found in mice in a National Toxicology Program study for which results were released this year (See Feb. 6, Page 2).

The other agency risk assessment is by the EPA Office of Health and Environmental Assessment (OHEA), for which a draft was reviewed last week by the advisory committee. Industry objections were summarized by a committee member, former chairman of the committee Herschel Griffin, of the San Diego State University, who said in part:

> "The system of the International Agency for Research on Cancer (which EPA is attempting to adapt for its own cancer risk assessment policy -- See Nov. 21, Page 12) is not designed for regulatory purposes. 'Inadequate' human data may mean one of three things (including) that the studies did not show evidence of carcinogenicity. Some would call that a negative study. So we use the classification of IARC as 2B and wind up with the judgment that 1,3-butadiene is a 'probable human carcinogen.' And that is absolutely not true."

The draft OHEA assessment had said: "On the basis of sufficient evidence from studies in two species of rodents, and inadequate epidemiologic data, 1,3-butadiene can be classified, according to the IARC classification scheme, as a 'probable' human carcinogen, Group 2B. It was placed in subgroup B because of the inadequacy of the available epidemiological data. Using the newly proposed EPA classification scheme for carcinogenicity evidence, the ranking would be B2, meaning that 1,3-butadiene is a 'probable' human carcinogen."

Both CMA and the International Institute of Synthetic Rubber Producers (IISRP) challenged the "inadequacy" of epidemiologic data, referring to a study in eight styrene-butadiene rubber polymer manufacturing plants by G. M. Matonski, et al., of Johns Hopkins University and stating: "The EPA has been overly critical of the Matonski study but the study does have certain important strengths: (1) First, the methodology is sound. . . (2) Second, the study has more than adequate statistical power. . . (3) Third, the results were generally consistent among all eight plants involved in the study, and (4) The power and latency analysis of the study suggests that if significant mortality had been present, it would have been detected."

Stating that only 7,000 workers are potentially exposed to butadiene, as opposed to the 62,000 estimated by EPA, the institute said, "The EPA is still confusing previous epidemiology studies conducted within the rubber fabrication industry (non-butadiene related) with the only two studies devoted to the synthetic rubber production industry (butadiene related)."

The CMA also focused on animal studies in mice and rats, stating the NTP study in mice "overlooks the role of animal stress in influencing tumor formation." Also, said CMA, the NTP study "does not discuss the possible role of threshold mechanisms such as immunosuppression in initiating tumor development at high butadiene dose levels, does not acknowledge certain key findings of the Hazleton rat study which indicate that butadiene is a weak oncogen in the rat, and does not explore the possibility of interspecies differences."

A consultant to the advisory committee, Dr. James Bond of the Lovelace Foundation, Albuquerque, N.M., summarizing literature on 1,3-butadiene, noted that mice appear to metabolize the substance at about twice the rate of rats. Once absorbed, it appears to be widely distributed in tissues, he said.

Another consultant, Dr. Kenneth Brown of Computer Sciences, Inc., Research Triangle Park, N.C., said the chemical presents a "bewildering profile." Questioning why rat data were not used in the OHEA risk assessment, he said, "The mice got such a high rate of tumors and got them so fast, it may be appropriate to question whether this is an appropriate time interval to use."

Noting the uncertainty surrounding quantitative risk estimates, he said, "You've reached a precise level of uncertainty."

Committee member Dr. Marvin Kuschner, Dean of the State University of New York, Stony Brook, School of Medicine, said he didn't believe the mouse tumors could be "lumped together" as in the risk assessment and, "When you assume man is as sensitive as the most sensitive species, that's a value judgment that has to be justified in biology."

Committee chairman Dr. Richard Griesemer of Oak Ridge National Laboratory, said he agreed with Kuschner as to the inappropriateness of lumping all of the mouse tumor types together for the analysis and said, "By and large, there are only a few tumor types thought to be significant."

General Discussion of Risk Assessment Sounds Similar Themes

Similar themes were sounded in a general discussion of risk assessment as the American Industrial Health Council made a series of proposals and OHEA explained its methodology in some detail. OHEA pointed out that its estimates are "upper bound" estimates, with "true risk. . . close to the upper bound or significantly below it."

The committee was given a draft OHEA document, "Estimation of Lifetime Cancer Risks Using a Multistage Theory of Carcinogenesis," which represented the EPA Office of Research and Development's attempts to date to use more than the "linear" model in cancer risk assessment. The "internal review draft -- not to be construed to represent agency policy" -- advanced as an alternative assessment method an "average likelihood linear" method, which was said to have the advantage of "giving a better average estimate" and of being "less arbitrary than the 95% upper-bound method." The document said, "In addition, adoption of this method would demonstrate a willingness to use less conservative assumptions."

However, OHEA said, "This method would still overestimate risk when the linear terms are very small. The method also requires considerable calculations, and its theoretical mathematical justification is not clear."

The American Industrial Health Council introduced its comment on general carcinogenic risk assessment, saying important advances have been made in the understanding of mechanisms of cancer and that advisory committee review is one of the better ways of capturing such advances for governmental risk assessment. AIHC said in part:

"Risk assessment at regulatory agencies has relied heavily on the upper confidence limits projected by models for estimating low dose response. Agencies have been reluctant to make use of risk estimation procedures based on a characterization of human risk involving the total science data base, believing that the procedures were not scientifically proven, and that the more limited characterization erred on the side of safety. Recent developments in the scientific community have shown that assessments of risk more accurately reflecting scientific data and understanding than the use of an upper bound modeling result can be carried out. Inadequate and sometimes misleading reporting of agency risk assessments have shown that improved methods are needed to develop risk assessments that are sound and accurate, and as informative as possible to regulators and the public."

"AIHC would like to offer a number of positive suggestions for specific steps that could be taken by the regulatory agencies to improve their risk assessment methods and to strengthen the scientific bases for their regulatory decisions:

"1. The primary objective of dose-response estimation should be to develop the most reasonable or accurate estimate of response at low dose. A secondary objective should be to indicate the

possible error bands about the best estimate, often expressed as upper and lower confidence limits.

"2. Procedures used for low dose extrapolation should be consistent with all biological observations related to exposure to the chemical under study, including experimental data on mechanism of action, toxicokinetics, etc. . .

"3. Some measure of effective dose of the target organ, if available, should be used in the extrapolation procedures rather than administered dose. . .

"4. If mathematical models are used for estimating low-dose response, the results from several models incorporating different assumptions should be displayed, along with a discussion of their relationship to the data base for the substance under study. . .

"5. Estimates of risk derived solely from the linearized upper 95% confidence limit in the model currently used by the agencies should be described as an indication of relative high-dose potency, and it should be affirmatively stated that the calculated value is not an estimate of actual risk. In view of the linearized constraint in the model, the upper confidence limit values should not be described as 'plausible upper limits of risk' but as worst case estimates of what is likely not to occur. Misunderstanding of the meaning of such estimates has led to much public confusion.

"6. Primary emphasis should be placed on comparative metabolism, physiology and pharmacokinetics for selecting the best animal surrogate and procedure for cross-species extrapolation. . .

"7. Characterization of risk, the final step in the risk assessment process, is the multidisciplinary integration of all the data to characterize human risk. Risk characterization involves evaluation of the three steps in risk assessment: hazard evaluation, exposure assessment and low dose estimation. Data on mechanism of action and pharmacokinetics not incorporated into the dose-response estimate should be incorporated into the characterization of risk. Evidence of a cytotoxic mechanism, data from short-term tests for genotoxicity, information from multiple studies (negative and positive), and any other data on comparative metabolism and pharmacokinetics should be integrated by the use of expert judgment into the scientific characterization of risk.

"8. Agencies should frequently describe the types of data that are needed to provide the best evaluation of the dose-response function, and also indicate how such data will be used to estimate dose-response. . .

"9. Agencies should strengthen their use of effect review panels of independent scientists. Because the process of risk assessment relies upon sound, multidisciplinary scientific judgment, review by qualified scientists is essential to providing a sound scientific basis for regulatory decision-making."

Agency Promises Report on Priority Setting

The advisory committee questioned the priority of the work it is asked to do and was told that each of the EPA programs more or less establishes its own priorities. The advisory committee's reviews have concentrated for the most part on reviews sought by the Office of Air and Radiation, it was noted, although other offices have used the information.

"Priorities in selecting pollutants should be based on information available about exposures or potential exposure," said Dr. Edward Ferrand of the New York City Department of Environmental Protection, who headed a subcommittee of the health committee which reviewed the functions of the group.

The present system, said Dr. Kuschner, "sets up a kind of adversary system" in which members of the committee "take potshots" at EPA reviews. He also said prioritization is important.

A review of priority setting in EPA program offices and agency-wide was pledged to the subcommittee by EPA officials.

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DEALING WITH PESTICIDES IN GROUNDWATER CORE CONCERN OF APAC MEETING

Finding, evaluating and regulating pesticides in groundwater was one of the main concerns of EPA officials and members of the EPA Administrator's Pesticide Advisory Committee (APAC) at its April 11 meeting (See Feb. 27, Page 12; March 6, Page 2; March 13, Pages 12 and 13; and March 27, Page 16).

Some officials and Committee members seemed to think it would not be a good idea to add groundwater contamination as a trigger in the special review regulations (See April 3, Page 19).

Dr. John A. Moore, EPA's Assistant Administrator for Pesticides and Toxic Substances, commented that in many respects, the groundwater trigger would be a "me-too" one.

Richard Merrill, Dean, School of Law, University of Virginia, and former FDA General Counsel, asked how many pesticides would hit the trigger and then later suggested that it not be added.

Steven Schatzow, Director, OPP, EPA, predicted that all registered pesticides would be found in groundwater at least once and that therefore the trigger would add a number of pesticides to the list for special review.

Merrill said special review was a tool for the "hard case, not every case."

The agency's planned survey of pesticides in groundwater was discussed and the OPP Director noted that the study design would be presented to the public for comment.

Moore told the Committee that the study will cover about 48 pesticides in private and municipal water supplies and will cost $5 million-$6 million. Health advisory levels will be set on each of the 48, he said, adding that "all of the four dozen pesticides will be found in at least one water sample and we want to be able to say what it means." The design phase of the national study will be finished in mid to late summer, the EPA-er predicted.

The official said the study was not expanded beyond pesticides because of cost and because checks for industrial products would not be made in the same sampling locations as those for pesticides.

The purpose of the study is to "find the degree of pesticides in groundwater and why," Moore said.

Schatzow said that health advisory numbers would not be set for all pesticides because of a lack of data on a few of them.

Robert Koenig, Manager, Regulatory Affairs, Bar Soap & Household Cleaning Division, Procter & Gamble Company, said he was glad EPA was seeking public comment on the study design.