Scientific Developments in Risk Assessment: Legal Implications

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The legal community is faced increasingly with risk assessment data for a variety of issues including permits for facilities such as resource recovery plants; incinerators; hazardous waste disposal facilities; both new and old pesticide registration issues; compliance issues at the federal, state, and local levels; the extent of site remediation required to reduce risk associated with abandoned waste sites or even currently operated corporate facilities; and liability cases involving exposures to toxic chemicals. At the heart of these issues is the theoretical level of risk associated with both human and environmental exposures—theoretical because it is very rare that the association of exposure and injury can be defined with certainty. The current trend in risk assessment research is toward developing a more solid scientific basis for estimating both the likelihood of harm and the magnitude of the risk associated with past, current, and future exposures. This paper focuses on recent advances in the science of risk assessment that may be helpful in more accurately evaluating real risk.

The fear of underestimating risk and the general lack of acceptance of risk-based policies dominated the risk management area over the past decade, during which risk assessment was first used to assess the health effects of toxic chemicals. These concerns, coupled with a paucity of research data for improving risk assessment, led to statements of upper-bound risk based on worst-case exposure estimates. The practice of risk assessment over the last dozen years, however, has contributed a solid scientific basis for providing more accurate risk estimates. Important progress has been made in defining better approaches to dose-response mod-

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eling[1] and exposure assessment,[2] which in turn has led to predictions of considerably lower risk than those initially described as upper-bound. In presenting the recent advances in the science of risk assessment, this paper illustrates how conservative risk assessments can be replaced with more solidly-based scientific approaches that, on the whole, more realistically describe risk. This information can be critical to legal decisions that must rely on the scientific foundations linking property damage, personal injury and ecological harm to chemical and radioactive exposures.

I. WHENCE CAME CONSERVATISM?

In 1975, the Environmental Protection Agency (EPA) convened the first committee to confront the problem of reducing exposures to suspected carcinogens to a level associated with zero risk. This committee considered the risk assessment process used for radiation-induced cancer risk and developed guidelines to assess risk associated with exposure to suspected chemical carcinogens.[3] This approach was the first admission that a major federal regulatory agency was willing to accept some risk associated with carcinogen exposure. Yet, every effort was made to avoid underestimation of risk; wherever there was scientific uncertainty, the most plausible but conservative assumption was chosen. For example, indications of cancer responses in animals were given considerable weight without carefully evaluating whether the tumors observed at high dose levels were relevant to lower environmental exposure levels.[4] Furthermore, the dose-response

1. Dose-response modeling refers to the extrapolation procedure to estimate the responses that might occur in humans from low-dose exposure from observed responses in either animals or humans at considerably higher exposure levels.

2. Exposure assessment is the evaluative process of estimating how much total body exposure an individual might receive from all sources of potential exposure in the environment. For example, exposure can occur from inhalation, ingestion, or dermal absorption. The assessment process usually combines some actual measured data of chemical contamination with estimated levels of exposure using mathematical models to determine the transport and fate of chemicals in the environment and either measured or estimated absorption factors to evaluate total human exposure.

3. EPA Interim Procedures and Guidelines for Health Risks and Economic Impact Assessments of Suspected Carcinogens, 41 Fed. Reg. 21,402 (1976); EPA Guidelines for Carcinogen Risk Assessment, 51 Fed. Reg. 33,991 (1986) (proposed September 24, 1986).

4. Editorial, Seventeen Principles About Cancer, or Something, Lancet (March 13, 1976); National Cancer Advisory Board Subcommittee on Environmental Carcinogens (NCABSEC), *General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances: A Report* 58 J. NAT'L CANCER INST. 401 (1977).

modeling used a linear nonthreshold assumption to establish a plausible upper-bound on risk.[5] Many other conservative assumptions were made; for example, converting animal data to human data. To define the maximum plausible level of chemical exposure to an individual, exposure assessments likewise were based on a series of conservative assumptions including a continuous lifetime exposure, *i.e.*, for 70 years. The goal in 1976 was to perform risk assessments using these conservative assumptions while continuing the search for more accurate evaluations through further research and data development. This was especially true whenever the plausible upper-bound assessment affected a particularly difficult decision in terms of social and economic cost. In the majority of cases, however, this additional work was never completed, leaving the upper-bound risks as the only risk descriptions available. Upper-bound risks were particularly helpful in sorting the important health risk from the unimportant but a more definitive understanding of the actual public health threat was necessary to provide a clear basic environmental remediation.

Increasingly, scientists involved with risk assessment are now being asked to characterize risk more accurately for a host of environmental and occupational concerns that may have enormous economic and social consequences. The acceptance of risk assessment as a necessary process and the need for more realistic evaluations have led to greater research in the risk assessment field. Improvements in risk assessment have resulted from the collection of better data, the adoption of improved approaches, and the incorporation of better biological data to provide quantitative expressions of risk.

II. How is Risk Assessment Becoming Less Conservative?

Historically, protective assumptions replaced uncertainties; in some cases, uncertainty is now being replaced by improved scientific information. Solidly developed scientific approaches can provide public policy officials with the needed assurance that

5. Linear nonthreshold assumption refers to the assumption that a single molecule of a carcinogen can initiate the cancer process at the cellular level in such a way that the cell proceeds to a cancer endpoint. This assumption assumes therefore that there is some risk associated with even very low levels of exposure and that the relationship is a one-to-one relationship, *i.e.*, a linear relationship.

the magnitude of a public health problem is not being underestimated.

There are five primary areas of scientific development in risk assessment, the development of: weight-of-evidence, biological models, pharmacokinetic models and the reevaluation of threshold effects and exposure assessment. The first three apply to the so-called nonthreshold effects associated with suspect carcinogens. The other two relate to non-cancer endpoints and the broad area of exposure assessment.

A. *Weight-of-Evidence*

The first area of development explores whether or not responses at high doses should be factored into weight-of-evidence determinations without regard to their relevance to environmental exposure levels.[6] For example, in the Carcinogen Assessment Group's risk assessment of ethylene thiourea (ETU), the uniqueness of the observation of rat thyroid tumors was discussed in the context of threshold levels, namely, that these tumors resulted from suppression of thyroid activity only after the administration of a high enough dose.[7] This result is being examined to determine whether environmental exposure levels are likely to approach those that could be expected to elicit the rat thyroid tumor response; if not, only the mouse liver tumor response becomes relevant in the weight-of-evidence determination for environmental exposure levels. Results of other studies on different chemicals are similarly being reviewed for their relevance to human

6. This consideration was absent in the Guidelines for Carcinogen Risk Assessment. *See supra* note 3. Weight-of-evidence determination refers to the evaluative process first defined in the EPA cancer assessment guidelines of 1976 which takes the position that only rarely are human carcinogens defined by the human experience but more often must be defined by circumstantial evidence derived from animal studies and other information that may involve short term *in vivo* or *in vitro* studies, association with families of chemicals known to be carcinogenic and any other related information. The nature and strength of the circumstantial evidence has been described as ranging from a weak signal, *i.e.*, a weak weight of evidence to a strong signal, i.e., a strong weight of evidence. Thus, the weight of evidence determination is a qualitative determination that evaluates the strength of a signal derived from all existing data to define the likelihood that an agent may be a human carcinogen.

7. EPA Carcinogen Assessment Group, Preliminary Report on Ethylenebisdithiocarbamate (EBDC) (1977).

exposure because of tumor type observed, dosing levels used or metabolic and pharmacokinetic differences.[8]

B. *Biological Models*

In the second area of development, scientists and regulatory bodies are seeking a biological basis for the development of more accurate estimates of risk expected to occur at environmental exposure levels.[9] This effort represents a substantially different approach from routinely applying empirical formulas to estimate low dose responses from high dose data and focuses attention on the importance of research data that may guide low-dose modeling efforts. Such an approach at a minimum supplements plausible upper-bound expressions, thereby providing the regulatory or legal arena with an indication of the extent to which the plausible upper bound may be overestimating risk for particular chemicals. Early efforts to define more accurate estimates of risk began at EPA in early 1985. One product of this effort is the development of a generic approach using a two-stage framework which can incorporate biological information relevant to the relationship between dose and cancer causation.[10] This model adapts the clinical observations of Moolgavkar and Knudson to parameters involving exposure to toxic chemicals.[11] The effort was first undertaken by EPA's Risk Assessment Forum, and was ultimately published in the Journal of Risk Analysis in early 1987.[12]

8. *See, e.g.*, M.E. Andersen, Clewell, Gargas, Smith, & Reitz, *Physiologically-based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride*, 1987 TOXICOL. APP. & PHARM. 185-205; EPA Dioxin Task Force, A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD, (1987) (external review draft); T. Levine, W. Marcus, C. Chen, A. Rispin, H. Gibb & C. Scott, Special Report on Ingested Inorganic Arsenic: Skin Cancer; Nutritional Essentiality (1987) (prepared for the Risk Assessment Forum EPA, Washington D.C.);Thorslund & Charnley, *Quantitative Dose-Response Models for Tumor Promoting Agents*, in BANBURY REPORT 31: CARCINOGEN RISK ASSESSMENT: NEW DIRECTIONS IN THE QUALITATIVE AND QUANTITATIVE ASPECTS (1988); C. Travis, *Pharmacokinetics*, in CARCINOGEN RISK ASSESSMENT (1988); Moore, Recommended Agency Policy on the Carcinogenicity Risk Associated with the Ingestion of Inorganic Arsenic (September 18, 1987) (Memorandum to Lee M. Thomas); Shabecoff, *EPA Reassesses the Cancer Risk of Many Chemicals*, N.Y. Times, Jan. 4, 1988 at A1.

9. *See, e.g.*, Thorslund, Brown & Charnley, *Biologically Motivated Cancer Risk Models*, 7 RISK ANALYSIS 109 (1987); Thorslund & Charnley, *supra* note 8.

10. Moolgavkar & Knudson, *Mutation and Cancer: A Model for Human Carcinogenesis*, 66 J. NAT'L. CANCER INST. 1037 (1981); Thorslund, Brown & Charnley, *supra* note 9.

11. Moolgavkar & Knudson, *supra* note 10.

12. Thorslund, Brown & Charnley, *supra* note 9.

Thus far, EPA has proposed two important decisions in line with the trend toward less conservatism in dose-response modeling.[13] Basing its decisions on modifications in dose-response calculation methodology and better estimates of the exposures involved in the epidemiology studies, the Risk Assessment Forum has recommended lowering the arsenic ingestion potency by approximately an order of magnitude.[14] Further reduction by an order of magnitude is also being considered to reflect the limited likelihood of inducing lethal cancer;[15] while arsenic induces malignant lung cancer by inhalation, skin cancer has been the primary end point reported for ingestion.[16] Of course, this decision raises the issue as to whether or not survival and treatability should routinely be considered as part of potency reevaluations. In addition, EPA at one point proposed to downgrade the potency estimate for dioxin, which was initially derived using the linearized multistage model, by an order of magnitude.[17] This proposed adjustment relied on several factors, including the results of applying a tumor promoter model that had been developed for dioxin from the earlier two-stage model reported by Thorslund et al.[18] The model was based primarily on observations that dioxin seemed capable of promoting preneoplastic cells to rapidly replicate, probably by a mechanism that does not involve direct interaction with DNA. This model was verified by predicting the outcomes of other experimental studies.[19] Similar approaches have been applied to the termiticides chlordane and heptachlor, as well as methylene chloride. These approaches decrease the potency estimates at low doses by three or more orders of magnitude and could probably be applied to other chemicals that appear to promote high background tumor rates.

13. Both of these decisions are discussed in Shabecoff, *EPA Reassesses the Cancer Risk of Many Chemicals*, N.Y. Times, Jan. 4, 1988, at A1, col. 6.

14. T. Levine, W. Marcus, C. Chen, A. Rispin, H. Gibb & C. Scott, *supra* note 9.

15. J. Moore, Recommended Agency Policy on the Carcinogenicity Risk Associated with the Ingestion of Inorganic Arsenic (September 18, 1987) (memorandum to Lee M. Thomas).

16. Tseng, Chu, How, Fong, Lin & Yeh, *Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenicism in Taiwan*, 40 J. NAT'L. CANCER INST. 453 (1968).

17. EPA Dioxin Task Force, *supra* note 8.

18. The linear promoter modeling approach had been recommended by EPA's Science Advisory Board. *See* Thorslund, Brown & Charnley, *Biologically Motivated Cancer Risk Models*, 7 *Risk Analysis* 109 (1987); Thorslund & Charnley, *Quantitative Dose-Response Models for Tumor Promoting Agents*, *supra* note 8.

19. Telephone interview with T.W. Thorslund (February 4, 1988).

Additional applications of the biological model have involved the polycyclic organic compounds.[20] The practice of using the potency of benzo[a]pyrene as a unit equivalency to all other potentially carcinogenic polycyclic organic compounds greatly overestimates risk. This practice has continued in spite of the fact that comparative potency methods have been developed for other chemical classes, such as the dioxins. When assembled in the aggregate, several laboratory studies provide a more substantial basis for developing a comparative potency approach for polycyclic aromatic hydrocarbons (PAHs).[21] In addition, the shape of the dose-response curve for benzo[a]pyrene itself has been reevaluated.[22] Benzo[a]pyrene is a genotoxic agent as indicated by a linear rate of DNA adduct formation that parallels exposure. The tumor dose-response data do not parallel DNA adduct formation, however, but appear to fit a quadratic equation, indicating that two events are probably necessary to induce the response. EPA's initial cancer potency estimate for benzo[a]pyrene does not reflect this relationship.[23] The comparative potency approach for other polycyclic compounds, together with the revised dose-response curve for benzo[a]pyrene, has been used to accurately predict tumor outcomes in bioassays of chemical mixtures, which is not possible using upper-bound estimates.[24]

Another example of a chemical that may require two events to produce a cancer outcome is benzene. Current investigations examining the mechanistic data, indicate that benzene causes chromosome damage thought to be responsible for the chromosomal deletions and rearrangements observed in leukemia patients.[25] This relationship implies that, although linearity (a one-hit

20. *See e.g.*, Clement Associates, Inc., Comparative Potency Approach for Estimating the Cancer Risk Associated with Exposure to Mixtures of Polycyclic Aromatic Hydrocarbons (1988); T. Thorslund, G. Charnley & E. Anderson, Innovative Use of Toxicological Data to Improve Cost-Effectiveness of Waste Cleanup (December 1-3, 1986) (presented at Superfund '86: Management of Uncontrolled Hazardous Waste Sites, Washington, D.C.).

21. M.M.L. Chu & C.W. Chen, Evaluation and Estimation of Potential Carcinogenic Risks of Polynuclear Aromatic Hydrocarbons (paper presented at the Pacific Rim Risk Conference, Honolulu, Hawaii, 1984) (available from the authors, U.S. EPA Carcinogen Assessment Group); T. Thorslund, G. Charnley & E. Anderson, *supra* note 20.

22. Clement Associates, Inc., *supra* note 20.

23. *Id.*

24. *Id.*

25. Thorslund, Hegner, Anver & Voytek, Quantitative Re-Evaluation of the Human Leukemia Risk Associated with Inhalation Exposure to Benzene (1988) (prepared by Clement Associates, Inc. for API, CMA & WOGA).

model),[26] may establish a plausible upper-bound on human leukemia risk from benzene exposure, a quadratic relationship (a two-hit model)[27] provides a statistically better fit to the observed epidemiological data and has a more plausible biological explanation than does the one-hit model and thus may provide a more realistic description of risk.[28] Should this turn out to be the case, the risk from low dose exposure to benzene would be considerably lower than previously estimated.

In addition to the two-stage model for cancer risk assessment, the Individualized Response Model (IRM) proposed by Sielken permits more accurate reflections of variations in susceptibility of populations at risk.[29] Particular distributions of susceptibility and background levels of chemicals within a population can be studied and directly incorporated into the model. This technique is useful for identifying risk levels that are protective of especially sensitive subpopulations of individuals.

C. *Pharmacokinetic Models*

A third area of development involves the use of metabolic and pharmacokinetic data to estimate actual levels of chemical exposure to target tissues.[30] These studies may make important contributions because past practices have assumed that exposures by inhalation, ingestion, and dermal absorption represent actual exposure; knowing, of course, that the relevant exposure is the actual exposure to the target tissue.[31] In many cases, the levels of chemicals to which humans are exposed environmentally are not

26. A one-hit model is an extrapolation model that assumes that only a single hit of a chemical is necessary to cause a cancer response. This model essentially defines the linear nonthreshold model.

27. A two-hit model assumes that two independent events are necessary to cause the cancer process and therefore differs from the one-hit model in that it is nonlinear at low doses.

28. *Id.*

29. Sielken, *Cancer Dose-Response Extrapolations*, 21 ENVTL. SCI. & TECH. 1033 (1987).

30. M.E. Andersen, Clewell, Gargas, Smith & Reitz, *supra* note 8. C. Travis, *supra* note 8; Ward, Travis, Hetrick, Anderson & Gargas, *Pharmacokinetics of Tetrachloroethylene* ___ TOXICOL. APPL. & PHARM. ___ (in press).

31. *See e.g.*, Anderson, *Perspective on Risk Assessment of Carcinogens*, in BANBURY REPORT 31: CARCINOGEN RISK ASSESSMENT: NEW DIRECTIONS IN THE QUALITATIVE AND QUANTITATIVE ASPECTS 281 (1988); Anderson & The Carcinogen Assessment Group, *The Use of Quantitative Approaches to Assess Cancer Risks*, 1983 RISK ANALYSIS; Patrick & Peters, Exposure Assessment in Setting Air Pollution Regulations: ASARCO, Tacoma, A Case Study (1985) (presented at the Society for Risk Analysis annual meeting, Washington, D.C.).

linearly related to the levels of the chemical or its derivatives that reach a target tissue and elicit an effect, leading to very inaccurate estimates of risk. Pharmacokinetic models provide a means to relate external exposure to a biologically relevant dose that can serve as input for dose-response models. A recent development in the area of pharmacokinetics is the use of the physiologically-based pharmacokinetic (PBPK) models.[32] By using actual physiological parameters such as body weight, cardiac output, breathing rates, blood flow rates, and tissue volumes to describe the metabolic process, PBPK models relate exposure concentrations to organ concentrations over a wide range of exposure intervals.[33] The physiological parameters are coupled with chemical-specific parameters and metabolic constants to predict the dynamics of a compound's movement through an animal system.[34]

Pharmacokinetic models have been developed for the widely used solvents methylene chloride,[35] tetrachloroethylene[36] and benzene,[37] as well as for the carbamate pesticides. For example, the concentrations of the active metabolite ethylene thiourea (ETU) produced from the latter were estimated chemically by essentially measuring the intake of pesticide and then chemically measuring how much was excreted; the difference was assumed to have been converted metabolically.[38] In many cases such as this, data actually exist that can relate biologically effective doses to biological endpoints observed. For ETU, data exist to describe dose-related increases in thyroid weight as a consequence of both pesticide and ETU exposure in the mouse.[39] When the dose-re-

32. See sources cited *supra* note 30.

33. *Id.*

34. C. Travis, *supra* note 9.

35. M.E. Andersen, Clewell, Gargas, Smith & Reitz, *supra* note 8.

36. Ward, Travis, Hetrick, Anderson & Gargas, *supra* note 30.

37. Personal interview with C. Travis (March 1988). *See generally* C. Travis, J. Quillen & A. Arms, Pharmacokinetics of Benzene (1989) (submitted to Toxicology and Applied Pharmacology).

38. E. Anderson, R. Albert, M. Anver, L. Erdreich, R. Magaw & J. McCann, Evaluation of the Weight of Evidence for the Carcinogenicity of Mancozeb and Ethylene Thiourea (ETU) (1988) (prepared by Clement Associates, Inc. for Rohm and Haas Co.).

39. Anver, Cohen, Lattuada & Foster, *Age-Associated Lesions in Barrier-Reared Male Sprague-Dawley Rats: A Comparison Between Hap:(SD) and Crl:COBS[R] CD[R] (SD) Stocks*, 8 EXP. AGING RES. 3 (1982); Bionetics Research Labs, Inc., *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, 1 CARCINOGENIC STUDY 159 (1968); Gak, Graillot & Truhart, *Difference de Sensibilities du Hamster et du Rat Vis-a-vis des Effects de L'Administration a Long Terme de L'Ethylene Thiouree*, 9 EUR. J. TOXICOL. 303 (1976); P. Goldman, H. Bernacki & D. Quinn, Mancozeb: Three-Month Dietary Toxicity Study in

sponse curves are superimposed, the difference accounts for the extent of metabolic conversion. This work indicated that the earlier metabolic conversion rates predicted from rat data and used for human dose-response extrapolation may have been too high by a factor of five.[40]

In some cases, simple body burden data[41] can buttress estimates of exposure gained from limited ambient monitoring and the use of dispersion models. For example, arsenic can be measured in urine as an indication that exposure has occurred. More sophisticated efforts are underway to use biological markers at the cellular level as indicators of both qualitative and hopefully quantitative exposure to toxic chemicals.[42]

An interesting new approach to pharmacokinetics-based exposure calculations has been proposed by Patterson and Mackay.[43] This approach is an extension of the fugacity method which has been widely used to calculate the distribution of a polychlorinated biphenyl (PCB) in various tissue groups after oral administration. The authors found that only one percent of the PCB reached the liver, which is the target organ for PCB-induced cancer in rodent studies.[44] When combined with estimates of bioavailability, these

Rats (1986) (unpublished report no. 85R-167, Toxicology Department, Rohm and Haas Co., Spring House, Pennsylvania); Graham, Davis, Hansen & Graham, *supra* note 30; Graham & Hansen, *Effects of Short-Term Administration of Ethylene Thiourea upon Thyroid Function of the Rat*, 7 BULL. ENVTL. CONTAM. TOXICL. 19 (1972); Graham, Hansen, Davis & Perry, *Effects of One-Year Administration of Ethylenethiourea upon the Thyroid of the Rat*, 2 J. AGRI. FOOD CHEM. 324 (1973); Green, *Mechanisms of Action of Antithyroid Compounds*, in THE THYROID (1978); Innes, Ulland, Valerio, Petrucelli, Fishbein, Hart, Pallotta, Bates, Falk, Gart, Klein, Mitchell & Peters, *Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Report*, 42 J. NAT'L. CANCER INST. 1110 (1969); G. O'Hara & L.J. Didonato, Dithane M-45 and Ethylene Thiourea (ETU): Three Month Dietary Study in Mice (1985) (unpublished report no. 80R-124, Rohm and Haas Co., Spring House, Pennsylvania); Ulland, Weisburger, Weisburger, Rice & Cypher, *Brief Communication: Thyroid Cancer in Rats from Ethylene Thiourea Intake*, 49 J.NAT'L. CANCER INST. 583 (1972); Weisburger, Ulland, Nam, Gart & Weisburger, *Carcinogenicity Tests of Certain Environmental and Industrial Chemicals*, 67 J. NAT'L. CANCER INST. 75 (1981).

40. E. Anderson, R. Albert, M. Anver, L. Erdlich, R. Magaw & J. McCann, *supra* note 39.

41. Body burden data are data derived from human levels of chemicals in the body, e.g., the levels of chlorinated pesticides in human adipose (fatty) tissue, in blood levels, bones, teeth, and hair.

42. F. Perera, BIOLOGICAL MARKERS IN RISK ASSESSMENT in CARCINOGEN RISK ASSESSMENT, 123 (1988).

43. Patterson & Mackay, *A Pharmacokinetic Model of Styrene Inhalation Using the Fugacity Approach*, 82 TOXICOL. APPL. & PHARM. 444 (1986).

44. *Id.*

pharmacokinetics-based exposure calculations can produce dramatically lower estimates of dose and, subsequently, risk.[45]

In summary, many opportunities have been missed to assemble important biological data that can greatly assist in chemical dose-response modeling. Improved dose-response models can be developed for many chemicals given existing data. However, additional research is important to continuing progress in this area.

D. *Threshold Effects*

The fourth development in risk assessment has been trends in dose-response modeling for so-called "threshold effects." For example, dose-response modeling of reproductive or neurological toxicity may be performed using a biologically based approach. Two important methods have been used to identify threshold doses for agents thought to cause disease only after a certain level of exposure has been reached. In the first case, human data are sometimes used. Attention has been focused, for example, on the ambient air quality criteria pollutants because the Clean Air Act requires the establishment of protective exposure levels for the "most sensitive" individual.[46] It is very difficult, however, to have a large enough group of individuals sensitive to low doses to clearly reach a consensus on the correct protective dose. In the absence of human data, the general practice for so-called threshold effects has been to use the level associated with no observed effect in animal studies and then to apply uncertainty factors to obtain a reference dose that can be regarded as adequately protective of humans.[47] Again, using all the biological data available, it may be possible to establish a biologically based dose-response curve for these effects. In such cases, the choice of a health protective level of exposure may be more clearly defined, even specific for particular subpopulation groups such as children or adults with health impairments.

45. Patterson & Mackay, *A Steady-State Fugacity-Based Pharmacokinetic Model with Simultaneous Multiple Exposure Routes*, 6 ENVTL. TOXICOL. CHEM. 395 (1987).

46. *See, e.g.*, EPA Air Quality Ambient Standards: Lead, Sulfur Oxide.

47. EPA Interim Procedures and Guidelines for Health Risks and Economic Impact Assessments of Suspected Carcinogens, *supra* note 3.

E. *Exposure Assessment*

Finally, current trends in exposure assessment research are also important to the risk assessment process. Recent reviews and editorials have defined the current practice of exposure assessment.[48] Contemporary exposure assessment draws on three general sources: direct measurement of the contact between the receptor and the chemical; prediction of exposure, which usually combines modeling, monitoring, and activity patterns; and reconstruction of exposures from body burdens using pharmacokinetics. The traditional practice in the absence of verifiable data has been similar to dose-response modeling in its approach, making choices that are protective of public health by estimating the maximum plausible exposure in the absence of more precise data. Most exposure assessments have described the maximally exposed individual by using generic dispersion models for air, surface water, and groundwater.[49] These approaches are practical approaches for widespread exposure estimation by regulatory agencies because it would be impossible for such agencies to evaluate site-specific parameters for every source in detail. For important cases, however, it is possible to estimate actual parameters that may refine the estimates obtained by generic modeling. An example is the Tacoma Smelter study conducted by EPA, in which exposure estimates were lowered about fifteenfold as a result of more accurate source modeling.[50] Similar reductions in risks have resulted from the incorporation of site-specific parameters for groundwater and surface water modeling.[51] Most often improvements in the site or case specific scientific data lead to lower risk estimation, though this is not always the case. For example, higher risks have resulted from the use of better deposition models for particulates, adding risk of volatile organic chemical dose for shower activities, and factoring in chemical conversions in the environment which can replace one chemical

48. Callahan, *Science and Exposure Assessment*, 21 ENVTL. SCI. & TECH. 1139 (1987); Severn, *Exposure Assessment*, 21 ENVTL. SCI. & TECH. 1154 (1987).

49. *See e.g.*, D. Patrick & W. Peters, Exposure Assessment in Setting Air Pollution Regulations: ASARCO, Tacoma, A Case Study (1985) (presented at the Society for Risk Analysis annual meeting, Washington, D.C.).

50. *Id.*

51. Anderson, *Perspective on Risk Assessment of Carcinogens*, *supra* note 31.

with another more toxic one (e.g. tetrachloroethylene conversion to vinyl chloride).[52]

Other developments in exposure assessment include consideration of the bioavailability of chemicals. Bioavailability reflects the ability of a chemical to desorb from a matrix (e.g., soil) as well as its ability to be absorbed across a biological membrane. For example, experimental studies by Poiger and Schlatter[53] and van den Berg et al[54] suggest that the bioavailability of 2,3,7,8-TCDD from a fly ash or soil matrix may range from fifteen to fifty percent (i.e., less than half the amount that is available from food). The initial assumption was that virtually 100% of the measured dioxin was biologically available, thus making the risk outcome considerably higher. Determination of bioavailability can be equally or even more important for other chemicals.

Another factor that can be used to refine exposure assessments is the treatment of nondetectable data.[55] When data collected under EPA-approved protocols on chlordane and heptachlor levels inside houses that had been treated with these termiticides were reviewed, chlordane and heptachlor were found to be below the detectable limit of the measurement methods a great majority of the time. Several different approaches have been used in the past to estimate what level of a chemical might be present if it is not detected.[56] These methods have ranged from using values of

52. S. Foster & P. Chrostowski, Inhalation Exposures to Volatile Organic Contaminents in the Shower (1987) (presented at the 80th Annual Meeting of the Air Pollution Control and Hazardous Waste Management Assoc., New York, N.Y., June 21-26, 1987, paper no. 87-42.6); P. Cline & D. Viste, Migration and Degradation Patterns of Volatile Organic Compounds 217 (1984) (National Conference of Uncontrolled Hazardous Waste Sites Proceedings); Parsons, Wood & DeMarco, *Transformation of Tetrachloroethene and Trichloroethane in Microcosms and Groundwater*, 1984 RES. TECH. 56.

53. Poiger & Schlatter, *Influence of Solvents and Adsorbents on Dermal and Intestinal Absorption of TCDD*, 18 FOOD COSM. TOXICOL. 477 (1980).

54. Van Den Berg, De Vroom, Van Greevenbroek & Olie, *Bioavailability of PCDDs and PCDFs Absorbed on Fly Ash in Rat, Guinea Pig, and Syrian Golden Hamster*, 14 CHEMOSPHERE 865 (1985); Van Den Berg, Van Greevenbroek, Olie & Hutzinger, *Bioavailability of PCDDs and PCDFs on Fly Ash after Semi-Chronic Oral Ingestion by Rat* 15 CHEMOSPHERE 509 (1986).

55. Nondetectable data are data that are defined by the limitations of a protocol to measure the presence of chemicals in the environment. For example, if the detection limit of a particular measurement protocol is at one microgram per cubic meter, then the protocol has no ability to determine whether or not the chemical which is being monitored is present at zero or at just under the nondetectable limit. Thus, these nondetectable data points are referred to as nondetectables and must be dealt with in assessing the likelihood that the chemical is present up to the level of detection.

56. Interview with James Falco (March 1989).

zero for nondetects to half of the detectable limit up to the detectable limit itself. More refined methods may be used that take a combined physicochemical-statistical approach to defining the likelihood that a chemical is present. For example, data employed this way for chlordane and heptachlor indicated a level that was approximately an order of magnitude lower than the value obtained by using half of the detection limit for nondetects, as is suggested by EPA.[57] Other parameters may be appropriate in individual circumstances such as using kinetic data to define exposure rather than assuming a seventy year constant exposure if the source of the contaminant has been removed or if the chemical is known to degrade or be transferred to another environmental medium.

Another area currently undergoing refinement in the field of exposure assessment is the evaluation of human activity patterns. This area draws on the disciplines of psychology, sociology, and anthropology to accurately define activities that could result in chemical exposure. As an example, in many cases of evaluating indoor air exposure, individuals are frequently assumed to be exposed twenty-four hours per day for seventy years (i.e., that they spent all of their time in the house and never moved). Recent research indicates that employed men spend an average of 13.4 hours per day and employed women an average of 15.4 hours per day in the house.[58] Additionally, census figures indicate that approximately twenty-five percent of the U.S. population changes dwellings in a five-year period.[59] Incorporating detailed information on this type of behavior can have an important impact on exposure estimates.

III. WHAT DIFFERENCE DOES IT MAKE?

The outcome of the risk assessment process is to describe the theoretical risk of injury associated with a particular exposure circumstance. If the theoretical risk is lowered by improving the scientific basis for risk assessment, then the impetus for remedial action may be considerably decreased. Thus, the importance of current trends in risk assessment research are critical to legisla-

57. EPA Exposure Assessment Methodologies for Hazardous Waste Sites, (presented at EMSL, Las Vegas).

58. NATIONAL RESEARCH COUNCIL, INDOOR AIR POLLUTANTS (1981).

59. BUREAU OF CENSUS (1986) Census Data.

tive initiatives, the regulatory process, and the legal arena because greater accuracy in risk assessment permits the identification of a clearer set of issues. For example, the need for remediation can be vastly altered by using more accurate risk and exposure estimates. In addition, meritorious and non-meritorious cases for permit applications, awards and liability cases, compliance issues, and registration issues may be clarified. In short, it does not matter whether the risk assessment process is a component of an issue being considered under environmental statutes, the Food, Drug and Cosmetic Act, the Occupational Safety and Health Act, the Consumer Product Safety Act, or state and local laws; the more precise the risk assessment, the easier it is for difficult decisions to be made.