Statistical Science
1988, Vol. 3, No. 3, 320–327

Scientific Origins of Incompatibility in Risk Assessment

Paul D. Anderson

Abstract. A comparison of the carcinogenic potency estimates for many chemicals reveals that different governmental agencies derive and use alternative estimates of a chemical's carcinogenic potency. This paper examines which steps in the process of deriving carcinogenic potency estimates (e.g., high to low dose extrapolation, bioassay choice, data set treatment, etc.) contribute to the differences within and between governmental agencies by comparing the details of the process of potency estimation for four chemicals (ethylene dibromide, polychlorinated biphenyls, tetrachloroethylene and tetrachlorodibenzo-*p*-dioxin). For three of these four chemicals all agencies used similar high to low dose extrapolation models and most of the incompatibility arose from selection and treatment of bioassay results. The comparison suggests that an inverse relationship exists between the potential contribution of a parameter to incompatibility and its actual contribution; the existing incompatibility between agencies represented by existing differences in potency estimates is dwarfed by potential incompatibility; and, some but not all, of the incompatibility can be reduced.

Key words and phrases: Risk assessment, carcinogen potency estimates, bioassay, incompatibility of risk assessment, environmental health policy, environmental risk.

INTRODUCTION

Risk assessment is now an integral part of the formulation of public policy. For environmental contaminants suspected of having nonthreshold effects, excess lifetime cancer risk is the human health end point of concern and that which usually drives concentration guidelines. Assessment of excess cancer risk involves multiple extrapolations having their foundation in the biologic sciences and statistics. Because of this foundation, cancer risk assessment is often also referred to as quantitative risk assessment, the implication being that the estimated cancer risk numbers are accurate and precise. Yet for a given chemical one can find several different estimates of excess cancer risk due to identical exposures to that chemical. This paper examines where some of these differences arise.

Simply explained, cancer risk estimates are arrived at by combining exposure to a given compound with the carcinogenic potency of that compound, where carcinogenic potency is a measure of how effective a compound is at causing cancer. Differences in cancer risk estimates could arise from either alternative exposure estimates, alternative potency estimates or both. Uncertainty in exposure estimates is often thought to be the major contributor to differences among cancer risk estimates. Derivation of potency estimates can also contribute to differences between estimates of cancer risk, however, and in some cases, if not many, contribute even more than uncertainty in exposure estimates.

This paper examines how much the process of potency estimation can contribute to the uncertainty about a cancer risk assessment, where some of the incompatibility originates and assesses the contribution of different steps of the process to the uncertainty. This is done by comparing the derivation of alternative potency estimates for four compounds (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, polychlorinated biphenyls, tetrachlorethylene and ethylene dibromide). The paper concludes by drawing some generalizations about incompatibility between potency estimates.

Paul D. Anderson is Manager, Risk Assessment Division, Environmental Research and Technology, 696 Virginia Road, Concord, Massachusetts 01742.

APPROACH

Using both International Agency for Research on Cancer (IARC) and United States Environmental Protection Agency (USEPA) evaluations of chemical carcinogens, a list of suspect human carcinogens was identified. From this list, chemicals were chosen for which numerous potency estimates existed, with which the author had some familiarity and for which the potency estimate derivation process was available and reasonably clear. The final list included ethylene dibromide (EDB), polychlorinated biphenyls (PCB), tetrachloroethylene (PCE) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin). The list excluded known human carcinogens.

For each of these four chemicals, as many previously published potency estimates by United States state and federal agencies as possible were located and reviewed. Canadian and European potency estimates were excluded from the comparison because of practical constraints; however, such a comparison would likely identify additional sources of incompatibility. Nor were all potency estimates derived by state and federal agencies included. Some were excluded because they used the USEPA Carcinogen Assessment Group's potency estimates, already included in the comparison, as the basis for cancer risk estimation. In some cases documents deriving potency estimates could not be located. In other cases potency estimates may be excluded because the search failed to identify them.

Once located, existing potency estimates for each chemical were reviewed and compared. New potency estimates were not calculated by combining the procedures and parameter choices of different agencies. This could have been done to derive extreme potency estimates that magnify the uncertainty and incompatibility but the intent of the paper is to report on the uncertainty and incompatibility that exists within the risk assessment process as it is practiced by state and federal agencies today.

A unit risk value was calculated for each potency estimate for a given chemical by multiplying all the potency estimates for that chemical by a constant dose of the chemical. The dose was chosen for ease of presentation of results. Because the dose of any given chemical is constant, the differences among unit risk values is representative of the differences among potency estimates. For each chemical the unit risk associated with each reviewed potency estimate was plotted. In the paper the terms unit risk and potency estimate are used interchangeably.

In the paper a distinction is made between a "bioassay" and a "data set." "Bioassay" is defined as the unanalyzed results of an animal cancer study. "Data set" is defined as the particular data used to generate a potency estimate. A data set represents how the results of one or more bioassays were selected, analyzed and treated, i.e., tumor site selection, interspecies dose conversion, incorporation of pharmacokinetic data, etc. Clearly, many data sets can be developed from a single bioassay. The steps at which incompatibility exists in development of a data set from one or more bioassays are discussed in the text.

The reader should note that if the dose-response curves predicted by a high to low dose extrapolation model are nonlinear, as in some cases they are, the differences in unit risk estimates reported in the paper will not be constant over all doses. As dose changes the difference between potency estimates will also change, generally increasing with decreasing dose. Further, differences due to incompatibility in a given step, i.e., bioassay choice, are not independent of choices made in other steps. For example, the magnitude of the difference between two potency estimates caused by use of alternative data sets when the linearized multistage model is applied, may change when the Weibull or logprobit model is applied to those data sets.

RESULTS AND DISCUSSION

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

Eleven potency estimates for TCDD were compared. Eight of the potency estimates were derived by the USEPA (USEPA, 1985a), two were derived by the Centers for Disease Control (CDC) (Kimbrough, Falk and Stehr, 1984) and one was derived by the Food and Drug Administration (FDA) (Miller, 1983). TCDD potency estimates were converted to unit risk values by multiplying the potency estimates by a dose of 10 fg of TCDD/kg body weight/day (1 fg = 1×10^{-15} g).

Unit risk values vary from 1.3×10^{-3} to 7.7×10^{-18}, a ratio of 1.7×10^{14} (Figure 1a). However, the potency estimates used by agencies for standard setting are all within an order of magnitude of one and another (represented by unit risk values with *filled circles* in Figure 1a). Derivation of the other TCDD potency estimates has been published in agency documents but these potency estimates are not used when setting environmental concentration limits.

A plot of unit risks using an identical data set but applying different high to low dose extrapolation models reveals that model choice accounts for more than 10^{13}-fold of this ratio (compare Figure 1, a and b), but that model choice accounts for *none* of the incompatibility between potency estimates used by agencies for standard setting (Figure 1b). All agencies used the linearized multistage or one-hit models for standard setting (USEPA, 1985a; Kimbrough, Falk and Stehr, 1984; Miller, 1983). For the particular dose and bioassay used to generate the unit risks for dioxin,

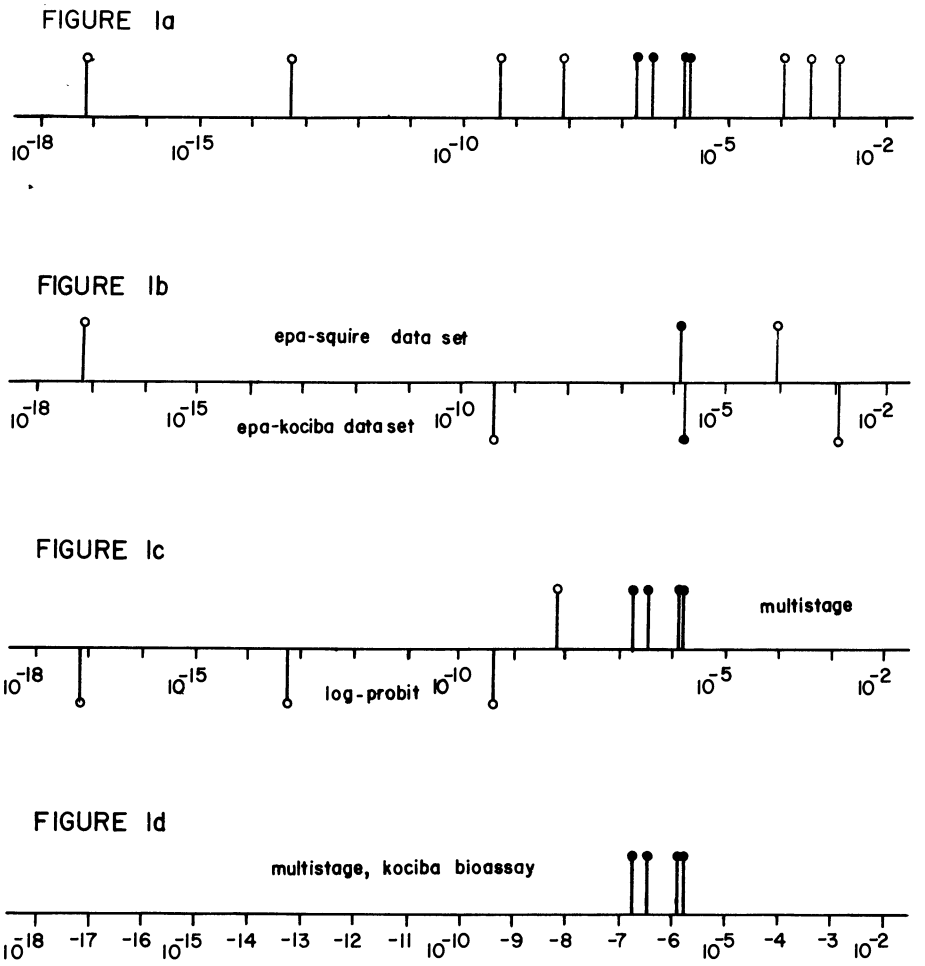


FIG. 1, a–d. *Unit risks for TCDD, calculated by multiplying TCDD potency estimates by a lifetime dose of* 10 *fg of TCDD/kg body weight/day, are plotted. The axes are log scale (to the base of* 10*) and the units are excess individual lifetime cancer risk. Unit risks derived from potency estimates used by agencies for standard setting are marked with filled black circles. In* a, *all* 11 *unit risk values are plotted. In* b, *unit risks calculated using the same data set but different models (Weibull, multistage, log probit) are plotted. Unit risks plotted above the axis were derived using one data set (USEPA,* 1985a, *Kociba analysis) and those plotted below the axis were derived using a different data set (USEPA,* 1985a, *Squire analysis). In* c, *unit risks derived using the same high to low dose extrapolation model but different bioassays are plotted. Unit risks derived using the multistage model and log probit models are plotted above and below the axis, respectively. Unit risks plotted in* d *were derived using an identical model (multistage) and bioassay (Kociba, Keyes, Beyer, Carron, Wade, Dittenber, Kalnins, Frauson, Park, Barnard, Hummel and Humiston,* 1978), *thus differences between potency estimates are due entirely to treatment of bioassay results.*

the Weibull model predicted the highest potency estimates, the log probit model the lowest and the multistage model predicted intermediate potency estimates (USEPA, 1985a).

Choice of bioassay contributes to incompatibility of dioxin potency estimates between agencies (Figure 1c). All agencies used results from the Kociba, Keyes, Beyer, Carron, Wade, Dittenber, Kalnins, Frauson, Park, Barnard, Hummel and Humiston (1978) rat bioassay. The CDC also used results from a National Cancer Institute/National Toxicology Program (NTP, 1982) mouse bioassay to estimate a lower limit on the range of excess lifetime cancer risk due to dioxin exposure. Because the CDC used the upper, and not the lower, limit to recommend allowable TCDD soil levels, all agencies used the same model and same bioassay to derive TCDD potency estimates for standard setting.

The difference of nearly an order of magnitude between the highest and lowest potency estimates when the same high to low dose extrapolation model and the same bioassay was used, arises from how agencies selected and treated bioassay results (Figure 1d). The largest difference, more than 5-fold, is due to incompatibility in conversion of dose between animals and man; some agencies converted on the basis of

surface area and others on the basis of body weight. Smaller differences arise from choice of tumor site, up to 3-fold; whether tumor incidence was regressed against administered dose or dose measured in the liver, up to 3-fold; and finally, which of two pathologists interpreted the incidence of tumors in tissue cross-sections, less than 2-fold.

Polychlorinated Biphenyl

The derivation of five PCB potency estimates were compared. Four were derived by the FDA (Cordle, Locke and Springer, 1982) and the other one was derived by the USEPA (1980). Unit risks for PCB were calculated by multiplying the USEPA potency estimate by a dose of 1×10^{-4} mg of PCB/kg of body weight/day and the FDA potency estimates by 0.0047 ppm of PCB in the diet because the FDA potency estimates are for ppm of PCB in diet. The two exposures are equivalent assuming a 70-kg adult consumes 1500 g of food/day (0.0047 mg of PCB/kg of food $\times$ 1.5 kg of food/person/day $\times$ 1 person/70 kg $= 1 \times 10^{-4}$ mg of PCB/kg of body weight/day).

A plot of unit risks for the five PCB potency estimates reveals a ratio of 44-fold between the highest (4.34×10^{-4}) and lowest (9.8×10^{-6}) (Figure 2a). Both agencies used models that produced identical results at low doses; the USEPA used the linearized multistage model and the FDA used the one-hit model (USEPA, Locke and Springer, 1980; Cordle, 1982). Thus selection of high to low dose extrapolation model does not contribute to the 44-fold ratio between potency estimates, however, model choice could increase the range among PCB potency estimates had the agencies published potency estimates using alternative extrapolation models. To date, the agencies have not done this and model choice does not contribute to interagency incompatibility.

The agencies used either the results of the Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse (1975) or the National Cancer Institute (NCI) (1978a) bioassays to derive potency estimates. Unit risks derived using each bioassay are plotted separately in Figure 2b (those using Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse (1975) are above the axis and those using NCI (1978a) are below the axis). Comparison of the lower end of the ranges shows that the potency estimates derived using the NCI (1978a) bioassay are slightly smaller than those based on the Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse (1975) bioassay, but that those based on the Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse bioassay virtually encompass the entire range of potency estimates derived using the NCI bioassay. Thus choice of bioassay can influence the potency estimate for PCB but as with TCDD, selection and treatment of bioassay results has the most important effect.

FIGURE 2a

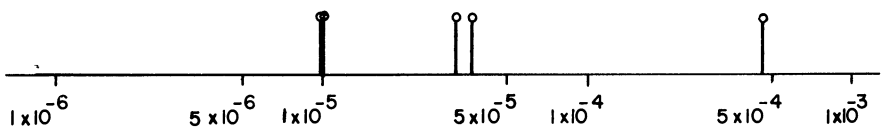
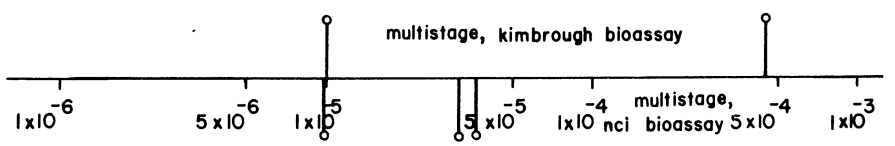


FIGURE 2b



EXCESS LIFETIME CANCER RISK (0.1 ug/kg/day)

FIG. 2, a and b. *Unit risks for PCB, calculated by multiplying PCB potency estimates by a lifetime dose equal to* 0.1 *μg of PCB/kg body weight/day, are plotted. The axes are log scale (to the base* 10*) and the units are excess individual lifetime cancer risk. All* 5 *unit risk values are plotted in* a. *Unit risks derived using identical models (multistage or one-hit) but different data sets are plotted in* b. *Unit risks above and below the axis were derived using results from Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse* (1975) *and from NCI* (1978a), *respectively. Differences between the unit risk estimates are due entirely to selection and treatment of bioassay results.*

PCB potency estimates using the Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse (1975) bioassay and the linearized multistage or one-hit model varied by 41-fold and those using the NCI (1978a) bioassay and the one-hit model varied by up to 4-fold. Incompatibility between potency estimates using the Kimbrough, Squire, Linder, Strandbert, Mondali and Bubse (1975) study is due to (1) regression of dose against alternative lesion sites, up to a 15-fold difference, (2) estimation of carcinogenic response based on a mg/kg dose or a ppm in diet dose, between a 3- to 4-fold difference; (3) adjustment, or lack of, for less than lifetime exposure of test animals to PCB, less than a 2-fold difference; (4) conversion of dose from animals to man on a surface area or weight basis, between a 5- and 6-fold difference; and (5) use of either a 95% or a 99% upper confidence limit of the potency estimate, about a 1.2-fold difference. Nearly all the incompatibility between potency estimates derived using the NCI bioassay (the unit risks plotted below the axis in Figure 2b) is due to choice of lesion sites.

Tetrachloroethylene

Eight potency estimates for PCE were compared. Two of these were derived by the USEPA (1985b) and six were derived by the Northeast States for Coordinated Air Use Management (NESCAUM) (NESCAUM, 1986). Unit risks were developed from PCE potency estimates by multiplying the potency estimate by an administered dose of 1 μg of PCE/kg of body weight/day.

Potency estimates for PCE vary by 43-fold (Figure 3a). The highest unit risk is 7.14×10^{-5} and the lowest is 1.68×10^{-6}. As with PCB, model choice does not contribute to the range between potency estimates because only the linearized multistage model was used to extrapolate from high to low doses.

Two bioassays were used. USEPA employed an NCI (1977) bioassay and NESCAUM used an NTP (1986) bioassay. When results from the two bioassays were treated similarly, the potency estimates derived using the NTP bioassay encompass those derived using the NCI bioassay. Thus bioassay choice makes a negligible contribution to incompatibility between PCE potency estimates.

Most of the incompatibility between PCE potency estimates is due to three steps in selection and treatment of bioassay results: lack of agreement about what values constitute standard temperature and pressure (STP), choice of lesion site and sex of test animal and the amount of administered PCE that is metabolized by different species when administered via different routes of exposure. Lack of agreement on STP has a negligible effect (less than 1.5-fold) on the range of

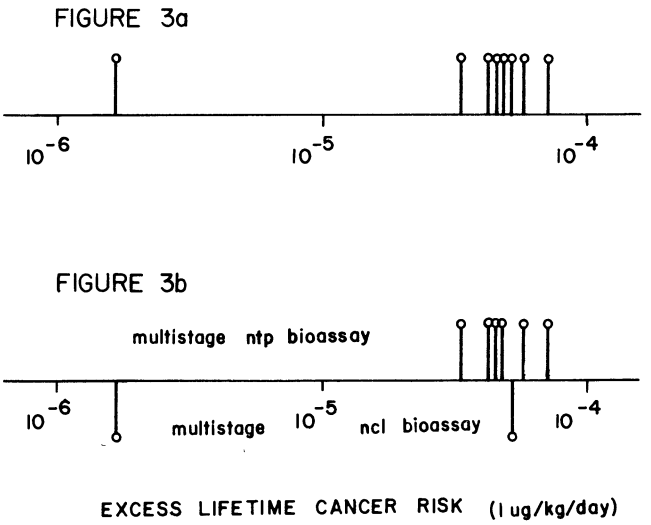


FIG. 3, a and b. *Unit risks for PCE, calculated by multiplying PCE potency estimates by an administered lifetime dose of* 1.0 μg *of PCE/kg body weight/day, are plotted. The axes are log scale (to the base* 10*) and the units are excess individual lifetime cancer risk. All eight unit risks are plotted in* a. *Unit risks derived using an identical model (multistage) but different data sets are plotted in* b. *Unit risks above and below the axis were derived using results from NTP* (1986) *and NCI* (1977)*, respectively. Differences between unit risks are due entirely to selection and treatment of bioassay results.*

potency estimates and led to only slight differences in the estimated amount of PCE inhaled by test animals. Choice of lesion site and sex of test animals accounts for a 2-fold difference between potency estimates derived using the NTP bioassay (Figure 3b, above axis). Different assumptions about metabolism account for the entire 30-fold difference between potency estimates derived using results of the NCI bioassay (Figure 3b, below axis). USEPA assumes 100% of the administered PCE via water is metabolized. When inhaled in air, however, USEPA assumes significantly less administered PCE is metabolized by humans. Thus the unit risk for PCE in air (1.68×10^{-6}) is much lower than the unit risk for PCE in water (5.1×10^{-5}).

Ethylene Dibromide

Eleven potency estimates for EDB were reviewed and compared. Two of the potency estimates were derived by USEPA (1983), eight were derived for the Occupational Safety and Health Administration (OSHA) (Brown, 1983) and one was derived by the National Academy of Sciences (NAS) (NAS, 1980). Unit risk values were calculated for EDB by multiplying the potency estimates by an administered dose of 1 μg of EDB/kg of body weight/day.

EDB is unique among the chemicals reviewed here in three aspects. First, a number of high to low dose extrapolation models were employed in deriving

potency estimates used to establish concentration limits. The increased complexity of some of the models, e.g., more parameters within the model that vary, made comparison of model effects difficult. Second, numerous bioassays have been conducted (NCI, 1978a, b; Wong, Winston, Hong and Plotnick, 1982; Olson, Habermann, Weisburg, Ward and Weisburg, 1973) and were used singly and together to derive potency estimates. Thus many combinations of bioassays and models were used in deriving potency estimates for EDB. Detailed comparison and quantification of the incompatibility at each step of the potency estimate derivation process was not possible for EDB because this required that for every parameter of interest there be at least two potency estimates in which all other parameters are held constant.

Third, EDB also differs from the other chemicals reviewed here in that its use, as a pesticide, has been largely suspended and therefore human exposure is expected to decrease. This along with unique laboratory results led to the use, by some agencies, of models of carcinogenesis dependent upon both magnitude and duration of exposure. The unit risks, based on lifetime exposure, calculated here for comparison of potency estimates were quite high in some instances and would have been substantially lower had a shorter duration of exposure been assumed.

A ratio of 4×10^6-fold exists between the highest (4.1×10^{-2}) and lowest (1.0×10^{-7}) unit risks (Figure 4a). Model selection accounts for a substantial proportion of the total incompatibility between potency estimates. The four unit risks plotted in Figure 4b vary more than 2000-fold and are derived using the same bioassay (NCI, 1978a, b), lesion site and species and sex of experimental animal, but different high to low dose extrapolation models. The two highest potency estimates were derived using the Weibull model and the two lowest were derived using the multistage model. Because data treatment also varied among the four potency estimates, i.e., animal to man dose conversion, statistical confidence limit of the potency estimate, adjustment for metabolism and dose against which tumor incidence was regressed, all the incompatibility cannot be ascribed to only differences in model choice.

Alternative methods of selection and treatment of

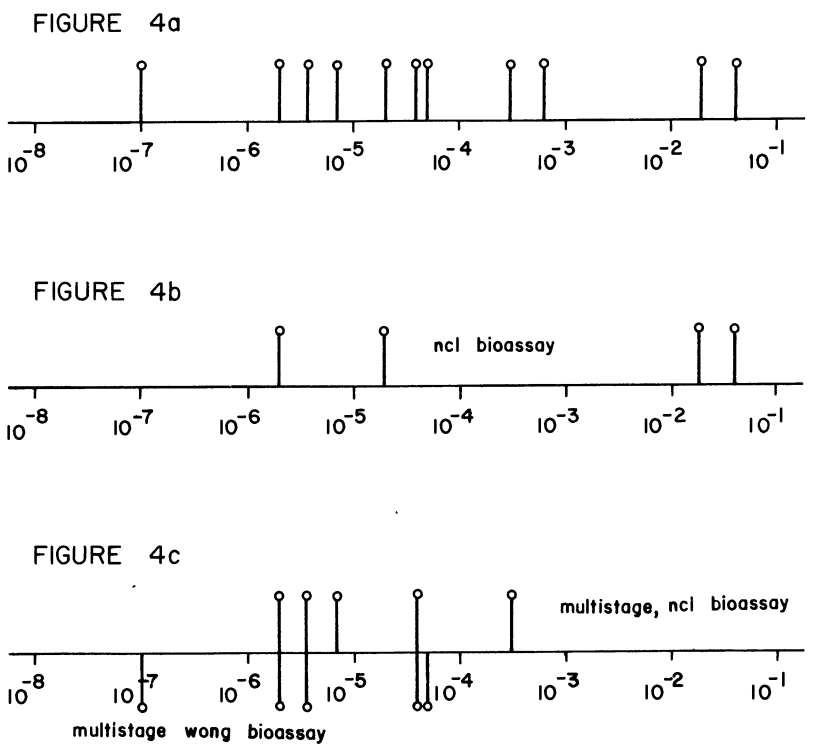


FIG. 4, a–c. *Unit risks for EDB, calculated by multiplying EDB potency estimates by a lifetime dose of* 1.0 *μg of EDB/kg body weight/day, are plotted. The axes are log scale (to the base* 10) *and the units are excess individual lifetime cancer risk. All eleven unit risk values are plotted in* a. *Unit risks derived using the same bioassay but different high to low dose extrapolation models and also different data sets are plotted in* b. *Unit risks derived using an identical model (multistage) and bioassay are plotted in* c. *Unit risks derived using results from NCI* (1981) *and Wong, Winston, Hong and Plotnick* (1982) *are plotted above and below the axis, respectively.*

bioassay results also contribute to incompatibility between EDB potency estimates. Using the multistage model and either the NCI (1981) bioassay (Figure 4c, above axis) or the Wong, Winston, Hong and Plotnick (1982) bioassay (Figure 4c, below axis) differences of up to 500-fold exist between the potency estimates and are due entirely to tumor site selection (Figure 4c).

CONCLUSIONS

1. An inverse relationship exists between a particular step's potential contribution to incompatibility between potency estimates and its actual contribution. Model choice could contribute most to the incompatibility between potency estimates used for standard setting, but with the exception of EDB, does not. Bioassay selection could make the next largest contribution to incompatibility between potency estimates, albeit much less than model choice, and does contribute to a portion of the range in some instances, but not to its full potential. Finally, the steps involved in selection and treatment of bioassay results have the smallest potential contribution to overall incompatibility, when compared for instance to the potential of model choice, but end up contributing the most and are the source of most of the incompatibility between potency estimates and agencies.

2. No agency consistently selected parameters at each step of the potency estimate derivation process that biased its potency estimate up or down. Thus existing incompatibility does not lead to as divergent potency estimates as it potentially might.

3. Incompatibility between potency estimates is reducible. At certain steps of the process agreement about what parameter to use should be attainable because evidence is either equivocal (as in conversion of dose from animal to man) or standards already exist (for example values for pressure and temperature at STP) or standards could exist, i.e., whether to use an upper 90%, 95% or 99% bound of the potency estimate.

4. All incompatibility cannot be eliminated. Decisions by scientists are influenced by values and past experiences. All of these cannot be eliminated or agreed upon. The best example of this is provided by TCDD where two pathologists examined the same tissue cross-sections and one pathologist counted 78% more tumors in control animals than the other pathologist (USEPA, 1985a). Some of this type of incompatibility is reducible but will never be entirely eliminated.

5. The incompatibility represented by the range in potency estimates used by agencies for regulation is small compared to the potential incompatibility and uncertainty that could result from, for example, use of different models of carcinogenesis. For most chemicals the potential uncertainties in estimation of carcinogenic potency are probably greater than uncertainities in exposure. Certainly an individual's potential exposure to dioxin does not vary by 2×10^{14}. The potency estimates for dioxin do and could vary by even more at low doses if the mechanism by which dioxin causes cancer has a threshold. A better method to quantify and express the uncertainty about potency estimates is also needed, not only to determine how great or small an excess cancer risk low levels of contaminants in the environment potentially pose to humans but also to assist regulators in setting priorities.

ACKNOWLEDGMENTS

The seeds of this project were sown in a risk assessment course taught by Dr. John Bailar. His continued insight and suggestions helped this project grow. This work was done while the author was a Fellow at the Interdisciplinary Programs in Health, Harvard School of Public Health, and was partially supported by USEPA Grant CR-807809.

REFERENCES

BROWN, D. R. (1983). Quantitative risk assessment for EDB. Northeastern Univ., Boston.

CORDLE, F., LOCKE, R. and SPRINGER, J. (1982). Risk assessment in a federal regulatory agency: An assessment of the risk associated with the human consumption of some species of fish contaminated with polychlorinated biphenyls (PCBs). *Environ. Health Perspect.* **45** 171–182.

KIMBROUGH, R. D., FALK, H. and STEHR, P. (1984). Health implications of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) contamination of residential soil. *J. Toxicol. Environ. Health* **14** 47–93.

KIMBROUGH, R. D., SQUIRE, R. A., LINDER, R. E., STRANDBERT, J. D., MONDALI, R. J. and BUBSE, V. W. (1975). Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Arochlor 1260. *J. Nat. Cancer Inst.* **55** 1453–1459.

KOCIBA, R. J., KEYES, D. G., BEYER, J. E., CARRON, R. M., WADE, C. E., DITTENBER, D. A., KALNINS, R. P., FRAUSON, L. E., PARK, C. N., BARNARD, S. D., HUMMEL, R. A. and HUMISTON, C. G. (1978). Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodiobenzo-*p*-dioxin in rats. *Toxicol. Appl. Pharmacol.* **46** 279–303.

MILLER, S. A. (1983). Prepared statement for Hearings before the Subcommittee of Natural Resources, Agricultural Research and Environment. Dioxin-The impact on human health. **78** 78–88.

NATIONAL ACADEMY OF SCIENCES (1980). *Drinking Water and Health* **3**. National Academy Press, Washington.

NATIONAL CANCER INSTITUTE (1977). Bioassay of tetrachloroethylene for possible carcinogenicity. PB-272940, Bethesda, Md.

NATIONAL CANCER INSTITUTE (1978a). Bioassay of Arochlor 1254 for possible carcinogenicity. DHEW Publ. NIH 78-838, Washington.

NATIONAL CANCER INSTITUTE (1978b). Bioassay of 1,2-dibromoethane for possible carcinogenicity. TR 86. DHEW Publ. NIH 78-1338, Washington.

NATIONAL CANCER INSTITUTE (1981). Carcinogenesis bioassay of 1,2-dibromoethane (inhalation study). TR 210. DHHS Publ. NIH 81-1766, Washington.

NATIONAL TOXICOLOGY PROGRAM (1982). Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (CAS No. 1746-

01-6) in Osborne Mendel rats and B6C3F1 mice (Gavage study). NTP Technical Report Series, Issue 209 195 NTP.

NATIONAL TOXICIOLOGY PROGRAM (1986). National Toxicology Program technical report of the toxicity and carcinogenesis studies of tetrachloroethylene (perchloroethylene). DHHS NIH Publ. 85-2567 (NTP TR 311).

NORTHEAST STATES FOR COORDINATED AIR USE MANAGEMENT (1986). NESCAUM regional evaluation document for tetrachloroethylene. Northeast States for Coordinated Air Use Management, Boston.

OLSON, W. A., HABERMANN, R. T., WEISBURG, E. K., WARD, J. M. and WEISBURG, J. H. (1973). Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. *J. Nat. Cancer Inst.* **51** 1993–1995.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (1980). *Ambient Water Quality Criteria for Polychlorinated Biphenyls.* EPA 440/5-80-068. Office of Water Regulation and Standards, Washington.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (1981). *Ethylene Dibromide: Position Document 2/3.* Office of Pesticide Programs, Washington.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (1983). *Ethylene Dibromide: Position Document 4.* Office of Pesticide Programs, Washington.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (1985a). *Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins.* EPA/600/8-84/14F. Office of Health and Environmental Assessment, Washington.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (1985b). *Final Health Assessment Document for Tetrachloroethylene (Perchloroethylene).* EPA-600/8-82-005B. Office of Health and Environmental Assessment, Washington.

WONG, L. C. K., WINSTON, J. M., HONG, C. B. and PLOTNICK, H. (1982). Carcinogenicity and toxicity of 1,2-dibromoethane in the rat. *Toxicol. Appl. Pharmacol.* **63** 155–165.