

to air particles. Furthermore, it appears that variations in metabolic genotype account for some of the interindividual variability observed in human biomarker studies. (This abstract does not necessarily reflect EPA policy)

586 HAZARD CHARACTERIZATION AND DOSE-RESPONSE ASSESSMENT OF CHLOROFORM: CASE STUDY USING EPA'S PROPOSED CANCER RISK ASSESSMENT GUIDELINES.

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The U.S. Environmental Protection Agency's (EPA) 1996 proposed cancer risk assessment guidelines are applied to the cancer hazard characterization and dose-response assessment of chloroform as a case study. Data from human studies, rodent bioassays, studies of genotoxicity, toxicokinetics, metabolism, cell proliferation, and mode of action are used to develop a weight-of-evidence determination that (1) chloroform carcinogenicity is secondary to high-dose target organ cytotoxicity/cytolethality and compensatory regenerative cell proliferation, and (2) these cellular events are likely to exhibit a threshold or dose range below which they will not occur. Therefore, a default assumption of nonlinearity and a margin of exposure/margin of safety analysis for dose-response assessment is warranted. A logistic regression model is employed to calculate measures of the central tendency and lower bound for the animal effective dose (i.e., ED₁₀ and LED₁₀, respectively). Doses are converted to human equivalent doses via either a default scaling factor or an interspecies adjustment based on pharmacokinetic/pharmacodynamic modeling data, and uncertainty factors are applied. A range of virtually safe doses (VSD) for drinking water exposure to chloroform can be estimated; these doses are orders of magnitude higher than those calculated by EPA using the linearized multistage model and EPA's 1986 guidelines.

587 ASSESSMENT OF MULTIPLE-PATHWAY POPULATION EXPOSURES TO WATER DISINFECTION BY-PRODUCTS.

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Population distributions of exposure to water disinfection by-products (DBPs) are being assessed as part of EPA's efforts to better understand and minimize health risks from microbial pathogens and DBPs in drinking water treated with chlorine or alternative disinfectants. DBP exposure occurs via multiple pathways (inhalation, dermal absorption, and ingestion) resulting from contact with various media (air, water, food). To model this exposure, human activity data are used to obtain patterns of movement and water usage which affect DBP exposure. Dermal contact with DBPs is estimated from these activity data. Multicompartment models are used to examine migration of airborne DBPs volatilized from water to indoor air in various rooms within a building. Data on ingestion of water, beverages, and foods, and their DBP contamination levels, are used to assess dietary exposure. Multi-pathway exposure assessments are linked to physiologically based pharmacokinetic (PBPK) models to estimate doses to target organs. Because activity patterns are not deterministic within the population, stochastic sampling of parameter values is used in the simulations to obtain distributions of exposures. Preliminary modeling results indicate that significant exposures occur through all three pathways.

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588 CHARACTERIZATION OF THE HEALTH RISKS TO TWO POPULATIONS OF ANGLERS WHO CONSUME DDT AND PCB COMPOUNDS IN FISH FROM THE PALOS VERDES SHELF.

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This paper presents an assessment of the theoretical risks to human health related to the consumption, by recreational anglers, of fish taken from the Palos Verdes Shelf or caught from the Cabrillo Pier within Los Angeles/Long Beach Harbor. The uptake of DDT, DDE, and DDD (collectively tDDT) and total PCBs due to fish consumption was characterized using MicroExposure Monte Carlo techniques. The MicroExposure Monte Carlo technique is a type of exposure analysis whereby lifetime exposure is estimated as the sum of doses received from individual exposure events, each of which is characterized using probabilistic methods. The MicroExposure

Monte Carlo analysis for Palos Verdes Shelf anglers made use of extensive site-specific data on local angler behavior and concentrations of chemicals in thirteen fish species or species groups. Upperbound cancer risks due to intake of tDDT and PCBs estimated using the MicroExposure Monte Carlo technique were on the order of 10⁻⁷ at the median and 10⁻⁶ at the 95th percentile. These results contrast with those from previous assessments for these anglers using the same underlying data wherein the risks estimated were 350 to 8,000-fold higher than those estimated using the MicroExposure Monte Carlo technique. The difference occurs because previous assessments relied on extrapolating short-term data to long-term exposures. In contrast, the MicroExposure Monte Carlo analysis uses the available data on the time scale for which they were collected and explicitly considers dependencies and correlations among exposure factors.

589 IMMUNOTOXICOLOGY: EXTRAPOLATION FROM ANIMAL TO MAN. ESTIMATION OF IMMUNOTOXICOLOGIC RISK ASSOCIATED WITH TBTO EXPOSURE.

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Exposure of rats to bis(tri-n-butyltin)oxide (TBTO) leads to deficient immune responses, and reduced resistance to infections, such as the parasite *Trichinella spiralis*. This effect on host resistance appears to be among the most sensitive parameters tested, as in rats exposed for a prolonged time (16.5 months) to 5 mg TBTO/kg food, no other effects of TBTO were observed. Internationally, this parameter has now been accepted to determine the no-effect-level for exposure to TBTO.

To elucidate the relevance of these observations in experimental animals, we have used the so-called parallelogram approach. According to this approach, the effect on host resistance in rats was extrapolated to the human situation, based on a quantitative species comparison of *in vitro* effects of exposure of rat and human peripheral lymphocytes. We choose human peripheral lymphocytes and rat peripheral (spleen) lymphocytes for this purpose, and used Concanavalin-A responsiveness as a measure of functionality, as the best proximate for immature T lymphocytes accessible both in rats and humans. *In vitro* exposure to TBTO was carried out at concentrations that did not affect viability. Dose-response curves were estimated, and the dose leading to a reduction of the functionality by 50% (Effective Dose 50, ED50) was calculated. Deviding the ED50 of human cells by that of rats resulted in an Inter Species Variability (IEV) factor of 3.18. In addition to interspecies variability, intraspecies variability was also accounted for. For this purpose the ED50 of the most sensitive sample of human peripheral lymphocytes was calculated and divided by the mean ED50 of all human samples, leading to a factor of 0.64. Similarly, the ED50 of the least sensitive sample divided by the mean ED50 was calculated to be 1.7. These figures were used as an indication for the upper and lower margin of the risk estimate of TBTO exposures. Based on dose-response curves on numbers of muscle larvae after infection with *Trichinella spiralis* in TBTO-exposed rats, we calculated that the dose of TBTO required to increase the larvae burden by 10% (expressed as numbers of muscle larvae per m² of striated (tongue) tissue), which in our view represents a clinically significant increase. This amounted to 0.39 mg/kg food. Hence, the calculated ED50 for the effect of TBTO exposure of humans on resistance to *Trichinella spiralis*, in humans ranged from (most sensitive individual) 0.39 x 3.18 x 0.64 = 0.79 mg to (least sensitive individual) 0.39 x 3.18 x 1.7 = 2.11 mg TBTO/kg food. A further step in the risk estimation should be the extrapolation of the daily intake in rats to the human situation. This assessment has not taken into consideration the particular vulnerability of the developing immune system. Hence, a next step should be to generate and use data concerning effects of TBTO on perinatal exposure.

The approach for estimating immunotoxicological risk as presented here may inhibit the need to use safety factors for inter and intra species extrapolation. It may serve to further understand in quantitative terms the risk of exposure to immunotoxic chemicals with respect to resistance to infectious diseases in humans.

590 USE OF RISK ASSESSMENT IN RISK MANAGEMENT DECISIONS: QUANTITATIVE UNCERTAINTY ANALYSIS OF RISK PARAMETERS.

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