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847 U.S. EPA's IRIS PILOT - PROVISIONAL UPDATED ASSESSMENTS OF NONCANCER AND CANCER TOXICITY FOR DIPHENYLMETHANE DIISOCYANATE (MDI).

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The inhalation reference concentration (RfC) for MDI is based on basal cell hyperplasia in the olfactory epithelium of chronically-exposed rats. The NOAEL, adjusted for duration of exposure, was identified at 0.036 mg/m³. Application of uncertainty factors to this value resulted in a provisional RfC of 2E-4 mg/m³. An oral reference dose (RfD) was not calculated inasmuch as MDI is insoluble in water. Overall confidence in the RfC was medium because of data limitations regarding reproductive parameters in laboratory animals and minimal characterization of human exposure scenarios. Based on U.S. EPA proposed guidelines, the carcinogenic potential of MDI is categorized as *cannot be determined, but there is suggestive evidence that raises concern for possible carcinogenic effects*. This assessment is based on the observation that methylene diphenyl aniline, a known animal carcinogen and reaction product of MDI, has been detected in body fluids of both laboratory animals and humans following MDI exposure. These assessments are based on information found in the supporting Toxicological Review of MDI.

848 CHEMICAL RISK ASSESSMENT AND MANAGEMENT REVIEWS: OXYRAMP.

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Chemical risk assessment and risk management are key elements of any product stewardship program. Our risk assessment and management program (OxyRAMP) was developed to identify, prioritize and address the health, safety and environmental issues for product lifecycles. OxyRAMP combines elements of the Chemical Manufacturers Association Product Risk Management Strategies document, a modified University of Tennessee hazard scoring and ranking procedure and an independently developed exposure assessment scoring system, into a formalized product risk management review. Key steps include: 1) formation of product review teams, 2) identification and collection of critical product information, 3) evaluation of physical/chemical properties and hazard information (includes persistence and bioaccumulation potential), 4) evaluation of lifecycle exposure issues and quantity/concentration estimates, 5) risk characterization, 6) risk prioritization, 7) evaluation of existing risk management systems, 8) identification of risk management actions and 9) establishment of a timeline for actions and future reviews. Program implementation is through business groups. Programs such as OxyRAMP help decrease risks associated with production, transport and sale of products, through improvements in risk management.

849 REVISITING ATSDR'S PUBLIC HEALTH HAZARD CATEGORIES: STEPS TOWARD BETTER PUBLIC HEALTH ASSESSMENTS.

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The Agency for Toxic Substances and Disease Registry (ATSDR) is charged with conducting Public Health Assessments (PHAs) of National Priorities List (NPL) sites, and may conduct similar assessments or consultations at other sites when petitioned to do so by concerned communities. These assessments and consultations reflect the professional judgement and discretion of the health assessors who compile and analyze data, draw conclusions, and make public health recommendations. Different health assessors have sometimes drawn different conclusions regarding the public health implications of the same environmental contaminant, depending upon whether those conclusions were based on (1) a rote algorithmic determination of risk (RAD), or (2) a thorough review of all the relevant toxicological data. ATSDR's Designated Reviewers Forum recently identified the current guidelines and criteria of ATSDR's Public Health Hazard Categories (PHHCs) as a potential source of these inconsistencies, and subsequently proposed revisions to those guidelines and criteria. The purpose of these proposed revisions was to (1) remove any and all implications that ATSDR's Minimum Risk Levels (MRLs) may be used as surrogates for thresholds of toxicity, (2) discourage reliance on RAD, and (3) encourage consideration of all relevant scientific information

available, as soon as it becomes available. The current and proposed Public Health Hazard Categories are compared and discussed.

850 HARMONIZING NONCANCER AND CANCER DOSE-RESPONSE METHODS.

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A consistent framework is proposed for evaluating scientific information and health policy considerations relevant to human health risk assessment. Harmonization is necessary to compare chemicals, maximize utilization of scientific information, and minimize potentially contradictory results with one chemical. Our harmonization framework consistently incorporates data or uses defaults for exposure-response, pharmacokinetics (PK), pharmacodynamics (PD), and science/policy issues. The first step reviews oral, inhalation, and dermal exposure dose-response studies to identify critical studies for all limiting toxicity endpoints. Next, supporting data are organized for use in subsequent steps. Mode of action data describing PK and PD in the species used in the toxicity study are then evaluated quantitatively. Pharmacokinetic information includes tissue time course data, physiologically based pharmacokinetic (PBPK) models or exposure dose defaults. Alternative dose metrics are evaluated and multiple default options should be available to describe reactive or stable compounds. Pharmacodynamic information would be incorporated using *in vivo* or *in vitro* data, modeling or defaults. Options for PD include threshold, nonlinear, and linear models as supported by data or defined for noncancer and cancer defaults. For animal toxicity studies, extrapolation to humans occurs next. Human exposure scenarios are reviewed defining potential human receptors (e.g. adults, children). Interspecies extrapolation of the mode of action considers PK and PD using data or defined defaults. Many issues currently in uncertainty factors or margin of exposure considerations will have already been incorporated. Those remaining would be addressed in the last step, such as human variability, severity of effects, and database limitations. As a wider range of scientific information is used, alternative risk assessment options are needed and must be organized into an overall format to promote consistency and comparability. Supported in part by the Chemical Manufacturers Association.

851 STOCHASTIC EVALUATION OF ACUTE INHALATION THRESHOLDS FROM REPORTED LOAELS.

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To estimate threshold doses for acute inhalation exposures, No Observed Adverse Effect Levels (NOAELs) are generally used. However, since NOAELs are often not available, Lowest Observed Adverse Effect Levels (LOAELs) divided by an uncertainty factor (UF) are often substituted. US EPA has recommended that a UF between 1 and 10 be used, and that it reflect the scientific judgment of the LOAEL to NOAEL difference. In practice, 10 has generally been used as the UF for standard setting. The purpose of this paper is to evaluate the distribution of the LOAEL to NOAEL ratios and to consider the importance of severity of the adverse effect in the evaluation. Data (quantal and continuous) from a number of different chemicals, and a variety of acute inhalation toxicity endpoints, were utilized in the analysis. LOAELs and NOAELs from reported studies were used to evaluate the lower range of the ratio. Other adverse effect levels in the reported studies were compared with the NOAEL to evaluate the upper range of the of the ratio. The ratio was also evaluated for lethal and non-lethal endpoints. The results indicate that a UF of approximately 3 to 5 would encompass the 95th percentile of results when calculating the LOAEL to NOAEL ratio within a severity category (e.g., discomforting, disabling and lethal categories), or when calculating the NOAEL for the least severe endpoint. However, an UF of 10 would encompass the 95th percentile when extrapolating from a lethal effect level to the lowest NOAEL. This relationship did not consider the effects of the intraspecies or intraspecies UFs, nor were the UFs to be used by other exposure routes or durations evaluated.

852 EVALUATION OF THE 10% ELICITATION THRESHOLD FOR CR(VI) IN TERMS OF MASS PER SURFACE AREA USING BENCHMARK DOSE METHODS.

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Historical patch test data have been used by the New Jersey Department of

Environmental Protection to develop soil cleanup levels for Cr(VI) protective of allergic contact dermatitis (ACD) in pre-sensitized individuals. These historical studies used a variety of patch testing methods and were performed before the standardization of diagnostic criteria for ACD. The dosimetric used in the historical studies was "concentration" rather than the more appropriate dosimetric for risk assessment of "mass per surface area". Recently, sufficient information from the historical studies have become available to convert dose levels from units of concentration to mass/area. For this study, benchmark dose methods were used to estimate the 10% minimum elicitation threshold (MET) based on the converted patch test data from these historical studies and from data presented in a more recent study by Nethercott *et al.* (1994). A truncated lognormal model was fitted to the data from each individual historical patch test study, from the Nethercott study, and from a combination of all of the historical studies using maximum likelihood methods. The 10% MET from the Nethercott study is much lower than those from the individual historical studies and all the data combined. The estimated dose-response curves show that the response rates in the Nethercott study are consistently higher than those from the historical studies suggesting that the study population of Nethercott may have been more sensitive to Cr(VI) than the historical cohorts, that improved diagnostic methods have reduced the potential for misidentifying irritant responses as allergic or the new TRUE™ Test patches have improved dose delivery.

853 ESTIMATION OF BENCHMARK DOSES FOR TRICHLOROACETIC ACID (TCA) AND COMPARISON OF THE RFD DERIVATION USING THE NOAEL/LOAEL METHOD AND THE BENCHMARK DOSE METHOD.

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The U.S. Environmental Protection Agency is investigating the use of a benchmark dose that may provide an alternative quantitative approach to the conventional no-observed-adverse-effect level/lowest-observed-adverse-effect level (NOAEL/LOAEL) for estimation of a Reference Dose (RfD). In this research, fetal dose response data from the Smith *et al.* (1989 Teratology 40: 445-451) study of Sprague-Dawley rats exposed to trichloroacetic acid (TCA) in drinking water during gestation days 6-15 were used to estimate benchmark doses. Three quantal models that included dose and litter size as the explanatory variables were used to estimate benchmark doses for fetal crown rump length and fetal body weight, after converting these continuous data to quantal form. These benchmark doses were compared to the benchmark dose for fetal visceral malformations from the same study estimated by Kavlock and Kimmel (1992, *in*: Risk Assessment of Prenatally-Induced Adverse Health Effects, Springer-Verlag, Berlin), using the same three models. Comparison of modeling results using extra risk estimates for the 95% lower confidence limit of doses at the 5% level of risk (LED05s) suggests that decreased fetal body weight was the most sensitive endpoint among those examined in this study. Derivation of a chronic RfD from the Smith *et al.* (1989) study using the NOAEL/LOAEL method is compared to the alternative benchmark dose RfD methodology using the LED05 for decreased fetal body weight. Although different uncertainty factors were used in these RfD approaches, the comparisons suggest that both the conventional method and the benchmark dose method to derive a chronic RfD for TCA from this developmental data arrive at similar RfDs.

854 GAMMA DISTRIBUTION ANALYSIS OF CHEMICAL CARCINOGENICITY.

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Bayes' theorem and Kolmogoroff's probability theory predict that an event will occur in the future as in the past given the constancy of conditions over time. Characterization of chemical carcinogenicity is a rosetta stone for the reduction of human cancer risks. There are 2 approaches for the identification of chemical carcinogens. Epidemiology provides a direct observation between exposure & the development of cancer. However, there are problems of long latency & low incidence of cancer in a population with overlapping age structure. In contrast, rodents offer well-defined genetic strains; ease in husbandry & experimentation under defined parameters for identifying the carcinogenicity of a chemical: time of exposure & an operationally well-defined MTD. A positive cancer response is concluded from a statistically significant increase in incidences of tumor bearing animals in treated in comparison

with the control group. More than 1 dose group in a trend, multiple species and multiple target organs strengthen evidence for human carcinogenicity. Tumor incidences over the life-time of rodent populations exposed to various tri-halomethanes were studied for gamma distribution parameters with moment & maximum likelihood estimates to provide new mechanistic information. This approach in the analysis of animal carcinogenicity promises us not only with new information of mechanism but may lead to a more reliable estimate of human cancer risk from exposure to a chemical. ((This abstract represents the authors' opinion and does not reflect the official position of USEPA)).

855 A MECHANISTIC APPROACH TO FORMALDEHYDE RISK ASSESSMENT INCORPORATING CELL PROLIFERATION AND AIRFLOW MODELING.

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Formaldehyde (HCHO) induced nasal squamous cell carcinomas in F344 rats exposed chronically to concentrations ≥ 6 ppm. Previous risk assessments based on the linearized multistage model used either the airborne HCHO concentration or the quantity of nasal DNA-protein cross-links as the measure of exposure but did not incorporate cell proliferation, which can play a critical role in the induction of tumors. The population-weighted *cell proliferation index* (unit length labeling index; ULLI) at specific sites in the rat nose is highly correlated with the incidence of squamous cell carcinomas at the same sites (T. Monticello *et al.*, *Cancer Res.* **56**, 1012, 1996). To better understand the relationship between cell proliferation and delivered dose, calculations of the amount of HCHO absorbed at specific sites (HCHO flux) were performed using FIDAP fluid dynamics analysis software. The ULLIs in several regions of the nose determined after 3 mo. of exposure to concentrations of 0.7, 2, 6, 10, or 15 ppm were compared with the HCHO flux in the same regions. The results showed no induction of cell proliferation at flux values < 0.8 fg/mm²/sec, but a site-specific proliferative response was induced at higher flux values. This response was nonuniform, *i.e.*, the ULLIs observed at individual sites differed at given values of the HCHO flux. The nonuniformity of this response may be related to differences in nasal mucosal structure or to changes in cell type from respiratory epithelium to squamous metaplasia during subchronic exposures to concentrations > 2 ppm. Differences and alterations in mucosal morphology could modulate the tissue concentration of HCHO either by changing the amount absorbed or by modifying its rate of elimination.

856 MECHANISTIC LINKAGE BETWEEN MULTISTAGE MODELS OF CARCINOGENESIS AND PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS.

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It is a common practice in using mechanistically-based mathematical models for carcinogenesis to develop a model for distribution and metabolism, calculate a summary measure of exposure from this model (eg. lifetime average of a key metabolic product) and use this value as the dose in a mechanistically-based cancer model. Until recently, this procedure was required since it was not possible to directly link stochastic cancer models to PBPK models in a way which allows the parameters in the cancer model to vary with time. Portier *et al.* (Mathematical Biosciences, 135:129-146, 1996) solved this problem by deriving tumor incidence from a stochastic cancer model through a set of ordinary differential equations. The method allows for time-varying rates in the cancer model as well as a much broader array of possible stages than has previously been considered. With this method, the effects of peak exposures, early life exposures, periodic exposures and other similar discontinuous patterns of exposure on cancer risk can be studied directly within the context of stochastic cancer models. In this presentation, the methods developed by Portier *et al.* (1996) are described and applied to sample data (dioxin, methylene chloride, primadone) to illustrate the utility of this approach for risk assessment. A commercially-available, graphically-based simulation language (Simulink) is used to illustrate the technique.