Summary Risk 1

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ORAL PRESENTATION

The risk posed by exposure to some persistent organochlorine pollutants (POPs) is currently best assessed and maneged by use of the Dioxin Toxic Equivalency Factor (TEF) approach. It has the obvious advantage to include mixtures of these compounds, given that the substances act with relative potency (REP) via a common mechanism, the binding to the Aryl hydrocarbon receptor (AhR). The TEF methodology assumes dose-additivity, but has never been evaluated for cancer risk. **Walker et al. 296** present a summary of four chronic rodent bioassays conducted by the National Toxicology Program (US Department of Health and Human Services) that evaluated the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 3.3',4,4',5- pentachlorobiphenyl (PCB126) and 2,3,4,7,8 pentachlorodibenzofuran (PeCDF) and a mixture of these three dioxin-like compounds in female Harlan Sprague Dawley rats, to to test the hypothesis of dose-additivity of carcinogenicity by a defined mixture of dioxin-like compounds. Based on these studies **Budinsky et al 595** provide important new information for evaluating the accuracy of TEFs in predicting the potential human cancer hazard for 4-PCDF and PCB126 alone and in combination with TCDD, a (presumably) equipotent mixture of these three compounds. They implicate that the current TEF of 0.5 for 4-PCDF, when combined appropriately with the new TCDD bioassay data, may slightly underpredict the results from the new 4-PCDF bioassay.
Haws et al 599 consequently point out that REP values typically represent a heterogeneous data set, for which it would therefore be helpful to better understand the degree to which the TEF values contribute to variability and uncertainty in the risk assessment process. As such, the topic of their presentation is the development of a database that will better characterize the range of REPs, allowing for better characterization of variability and uncertainty inherent in the mammalian TEFs. In their oral and their poster presentation **(** see also **Haws et al 602)** they provide recommendations regarding possible next steps for developing and interpreting a refined REP database for risk assessment purposes.
Moving from risk characterisation to exposure assessment **Aylward et al 370** present estimates of cumulative exposure to TCDD for occupationally exposed cohorts by integrating job exposure matrices based on work histories with measured serum lipid TCDD levels. Previously it was assumed that elimination of TCDD occurred via a first-order process with a half-life of 7.1 to 8.7 years, however recent studies have demonstrated that the elimination of TCDD occurs via a concentration-dependent process: elimination occurs at a greater rate when body concentrations are relatively high, with effective elimination half-lives of less than 3 years at serum lipid levels above 1,000 ppt. By means of a concentration- and age-dependent model of elimination (CADM) they modeled the job exposure matrix data for the cohort of TCDD-exposed chemical manufacturing workers studied by the U.S. National Institute for Occupational Safety and Health (the "NIOSH cohort"[1]). In their presentation they describe the process of exposure reconstruction, the impact of the CADM on dose estimates for the cohort, and the variability in the dose estimates obtained.

Edler et al 247 elaborate on the uncertainty of TCDD risk estimates, in which toxicokinetic model uncertainty carries over to risk estimate uncertainty and uncertainty of the dose-response relationship. The validity of the results rises and falls with that of the underlying model assumptions. Two potentially crucial model assumptions for estimating the exposure of a person are the assumption of lifetime constancy of total lipid volume (TLV) of the human body and the assumption of a simple linear kinetic of TCDD elimination. A Carrier-kinetic model has been suggested to link the TCDD elimination rate to the available TCDD amount in the body. As a consequence if exposure is estimated by assuming a linear elimination kinetic although a Carrier kinetic model actually holds, then high exposures in reality will be underestimated through statistical analysis and low exposures will be overestimated, respectively. Their study shows how such compression effects carry over into dose-response modeling and explores the implications on the resulting risk estimates.

Lonati et al. 315 emphasise ~~on~~ incorporating uncertainties into final risk estimates by the integration of the conventional procedure with a probabilistic approach, based on the utilisation of distribution functions for describing the variability of the input parameters, instead of single point estimates normally derived from the conventional deterministic applications. This approach is utilised for evaluating carcinogenic risk distributions associated to the uncertainty of the main emission parameters of stack gas PCDD/Fs from a waste to energy plant. Results are compared with values derived from conventional deterministic applications.

Hiester et al 37 demonstrate how much the dioxin-like PCBs contribute to the total WHO-TEQ and outline the implications for assessment thresholds and other regulatory purposes. In ambient air, dioxin-like PCBs can have a considerable contribution (60-90%) depending upon the underlying sources.

Conner et al 440 address the issue of naturally-occurring compounds in the human diet that can bind to the aryl hydrocarbon, or *dioxin* receptor (AhR) and activate the AhR signaling pathway, such as certain indole carbinols and their derivatives, heterocyclic aromatic amines, flavonoids, carotinoids, vitamin A derivatives (retinoids), and tryptophan metabolites, which in terms of TEQ is often greater than that associated with daily background intake of anthropogenic dioxins. They estimated that the daily TEQ dose of an indole carbinol from cruciferous vegetables, is likely to be over 10,000-fold greater than the daily dietary TEQ dose associated with the background intake of PCDD/Fs and PCBs. Further, when TEQ doses were expressed as accumulated body burdens or area-under-the-curve doses, which accounted for different biological half-lives, ICZ still constituted >95% of the total (internal) TEQ dose. It will be interesting to follow the discussion of the health-implication of these estimates, but it is important to note that while IC does bind to the AHR, it and other natural dietary compounds do not meet the WHO criteria for inclusion in the dioxin TEQ approach.

POSTER SESSION

In addition to their oral presentation **HAWS et al 602** provide details of the REP database in the poster session.

As an alternative to the no-observed-adverse-effect-level (NOAEL), the benchmark dose (BMD) approach was proposed for extrapolation of data from animal studies to the low dose human exposure situation. **Fattore et al. 422** apply the BMD methodology to evaluate dose-response data of seven chlorinated biphenyl (CB) congeners, some of which are *dioxin-like,* from subchronic dietary exposure studies in male and female Sprague Dawley rats. The objectives of the study are to evaluate the applicability of the BMD approach, and to compare the values derived from BMD and BMDL with those obtained from the conventional NOEL and LOEL approach.

Ogura et al 311 summarize the overall half-lives of congeners in humans as reported in the literature, and compares them with the half-lives due to fecal and sebum excretions, as estimated by data on the concentrations of congeners in feces and sebum in the literature. In addition, the overall half-lives of congeners for the general Japanese population are estimated from the data on dietary intakes and concentrations in the human body reported by the municipalities.

Zhao et al 287 In the past little was known on the POPs contamination status of the residents in mainland of China. To elucidate body burden of organochlorine compounds and factors associated with organochlorine levels of the residents in North China, the group performed life style questionnaire and collected breast milk specimens from North China. Their data underline that comprehensive monitoring of OPs and dioxins in foodstuff is necessary in rural areas to understand the sources of exposure.

Nouwen et al 322 This poster focuses on the quantification of the variation in the risk indices using a probabilistic approach for a residential area located in the neighbourhood of two waste incinerators. Sampling of soil, vegetables and eggs was carried out, and incorporated in the risk assessment. which was at first carried out by using a deterministic approach.

Puzyn 480 present certainly much appreciated in-silico data on Polychlorinated Naphtalenes (PCNs), another group of dioxin-like POPs. Some chloronaphthalenes elicit toxic effects similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and these similarities might be expressed by means of toxic equivalency factors (TEFs). Based on their results, theoretical TEFs for all possible chloronaphthalene congeners were estimated.

Kasuo Asao et al 578 investigated the interesting phenomenon of the limb malformations of monkeys in Japan , which seem to be associated with feeding of food for human. In this study, the relations between dioxin exposure and the limb malformations of macaque monkeys were estimated by the epidemiological and experimental studies.

Many studies have revealed that higher levels of these compounds have been observed in fish-eating birds, a top predator in aquatic food chains. In the poster **Naito 61**, a population-level ecological risk assessment of dioxinlike PCBs on fish-eating birds is presented to judge the need for risk management measures to protect aquatic wildlife from dioxinlike PCB contamination in Japan.