RISK III

Toxic Equivalency Factors (TEFs)

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1. Introduction

Several PCDDs and PCDFs, as well as some PCBs have been shown to exert a number of common toxic responses similar to those observed for 2,3,7,8-TCDD. There is strong evidence suggesting a common mechanism of action of TCDD and related compounds, based on the binding of these compounds to the Ah-receptor. Due to the fact that dioxin-like compounds normally exist in environmental and biological samples as complex mixtures of congeners, the concept of toxic equivalents (TEQs) has been introduced to simplify risk assessment and regulatory control. In applying this concept, relative toxicities of dioxin-like compounds in relation to TCDD (i.e. toxic equivalency factors, TEFs) are determined based on *in vitro* and *in vivo* studies. This approach is useful, but has its limitations due to a number of simplifications.

A number of different TEF-schemes have been developed for PCDDs and PCDFs, as well as for dioxin-like PCBs. Recognizing the necessity for a more consistent approach towards setting internationally agreed TEFs, the WHO-European Centre for Environment and Health and the International Programme on Chemical Safety, initiated a project to create a data base containing information relevant to the setting of TEFs, and, based on the available information, to assess the relative potencies and to derive consensus TEFs for PCDDs, PCDFs and dioxin-like PCBs. The determination of individual TEF-values requires expert scientific judgement.

In an initial stage, available data on the relative toxicities of dioxin-like PCBs were collected and analysed by Professor Ulf G. Ahlborg and his collaborators at the Karolinska Institute in Stockholm, Sweden. Following this data collection exercise, a consultation was held at WHO in Bilthoven in December 1993, at which the available data were discussed. The ultimate goal of the consultation was to analyse the data base in order to define general criteria for further development of a more comprehensive TEF approach and to derive TEFs for dioxin-like PCBs. The outcome of this consultation has previously been reported[1)].

2. TEFs for dioxin-like PCBs

Available data on the relative toxicities of dioxin-like PCBs with respect to a number of endpoints were collected and analysed. All the data were compiled into a computerized spreadsheet format consisting of more than 900 entries and about 50 variables (e.g. congener, effect, doses used, estimated TEF, etc.). The data included in the data base were selected using the following criteria: (1) at least one PCB congener studied, (2) TCDD or a PCB-reference (PCB 77, 126 or 169) also studied in the same experiment, or with the same experimental design by the same authors in another experiment, and (3) endpoints affected by TCDD or the PCB-reference. Depending on the data reported different methods

were used to calculate the TEFs. If possible, TEFs were calculated from dose-effect curves. When ED_{50}-values or similar values were reported, TEFs were determined from ratios of these. In some cases, TEFs were used as reported in the article. However, the results of several studies were reported in such a way that reliable TEFs could not be calculated. The main problems encountered with the reported data for calculating TEFs were: (1) ED_{50}-values reported although different compounds caused different maximal effect levels, (2) only one dose level reported, (3) data presented only as graphs, or (4) only a few, high dose levels studied.

The data gathered resulted in a wide range of TEF-values for most individual PCB congeners. For some congeners, there were apparent differences between *in vitro* and *in vivo* experiments, as well as between acute and subchronic/chronic exposures. By sorting the data on endpoint, it was obvious that the majority of the entries were based on enzyme-induction and body and organ weights. Based on the available data base, and recognizing that the setting of interim TEFs dictates the choice of values which are more, rather than less conservative in order to be protective of public health, TEF-values for 13 PCB congeners were recommended[1)]. The TEFs were based on studies with repeated dosing *in vivo* when available. When such data were lacking, TEFs were chosen based on single exposure studies, structure-activity considerations and data from *in vitro* studies.

3. Limitations of the TEF-concept

It was recognized that there are some important limitations to the TEF-concept and that the TEF-values should be developed and used with care. The TEF-concept assumes additivity for all dioxin-like compounds in a mixture, a phenomenon which has not been clearly demonstrated. Moreover, the concept assumes identical dose-effect curves for the critical effects in humans and the effects the TEFs are based upon. In addition, nondioxin-like PCBs have their own independent toxicities and PCB metabolites may also be critical confounders. Furthermore, great care will have to be exercised when evaluating effects that can be caused by multiple mechanisms (e.g. increased liver weight, tumour promotion).
There are obvious deficits in the data base which require additional experimental information. Studies should be conducted with multiple doses, repeated dosing, and endpoints relevant for human risk assessment. Whenever possible, TCDD should be included as a positive control.
The recommended TEFs have been developed for use in exposure scenarios. Different classes of TEF-values may be needed depending upon whether the considerations relate to intake, body burden, or ecological concerns.

4. Present project

The data base is currently expanded to include the PCDDs and PCDFs, and also other dioxin-like compounds which meet the criteria of Ah-receptor binding, identity of effects, structural similarity, and persistence (brominated analogs of the biphenyls, dioxins, and furans, halogenated naphthalenes and diphenyl ethers, and other related compounds).
In order to create a data base as complete as possible researchers are requested to send any new data suitable for calculating TEFs to Annika Hanberg, Institute of Environmental Medicine, Karolinska Institutet, Box 210, S-171 77 Stockholm, Sweden.

5. Reference

1) Ahlborg U.G., G.C. Becking, L.S. Birnbaum, A. Brouwer, H.J.G.M. Derks, M. Feeley, G. Golor, A. Hanberg, J.C. Larsen, A.K.D. Liem, S.H. Safe, C. Schlatter, F. Wærn, M. Younes, E. Yrjänheikki (1994): Toxic equivalency factors for dioxin-like PCBs. Report on a WHO-ECEH and IPCS consultation, December 1993. Chemosphere 28, 1049-1967.