TOXICOKINETIC LIMITATIONS IN THE PRESENT TOXIC EQUIVALENCY (TEQ) CONCEPT

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ABSTRACT

The present toxic equivalency (TEQ) concept contains some major drawbacks due to the lack of incorporation of toxicokinetics and metabolism. The influence of kinetics is discussed in detail for the use of semichronic studies and the occurrence of nonlinear combination effects. A new TEQ approach is suggested in which a combination of biological response and toxicokinetics must be used.

INTRODUCTION.

At present the relative toxicity of PCDDs and PCDFs is estimated by a toxic equivalency concept, in which the toxic potency of especially the 2,3,7,8-substituted congeners is related to the most toxic congener, 2,3,7,8-TCDD. The combination of this concept with a tolerable daily intake (TDI) of 2,3,7,8-TCDD or TCDD-equivalents (TEQ) for humans is presently the only methodology available for risk assessment. However, some of the present TEQ values are mainly based on experiments partly lacking the influence of toxicokinetics in their results. According to our opinion the adverse effect of these compounds is determined not only through the biological response but also by kinetics. The toxicological response can thus be considered as a consequence of the interaction between both mechanisms.

Presently a number of (in vitro) bio-assays are used to evaluate the relative toxicity of PCDDs, PCDFs, PCBs or mixtures of these compounds. These bio-assays quite often involve only a single compound administration, while the response of e.g. cytochrome P-450I related induction, is only observed after a short time period, during which kinetic influence can be considered neglectible for the most relevant PCDDs and PCDFs.

Moreover, the comparative toxicity data of semi-chronic studies with different 2,3,7,8-substituted PCDDs and PCDFs are difficult to compare due to considerable differences in kinetics and metabolism.

In addition the nonlinear antagonistic and synergistic interactions between PCDD/Fs and PCBs observed in some experiments can not be included in the present risk assesment using the TEQ concept.

In this paper we will present some serious drawbacks inherent to the present TEQ concept and derived risk assessments, due to the lack of incorporation of toxicokinetics and metabolism. Furthermore some suggestions will be given for future, more realistic, approaches.

Comparative semichronic studies have been done with several 2,3,7,8-substituted PCDDs and PCDFs during three months time periods (1). When using data of these studies to establish TEQ values for the different congeners, it should be considered that their elimination is very different. As a consequence of these differences in kinetics steady state conditions will be reached after different time intervals and with some congeners not within a 13 weeks experimental period

By using computer simulation based on experimental data we illustrate in figure 1 this problem for 2,3,7,8-TCDD, 2,3,7,8-TCDF and 2,3,4,7,8-PnCDF in rats. For this simulation published toxicokinetic data were used from experiments with these congeners and rats (2,3,4). These calculations show that e.g. 2,3,7,8-TCDF reaches a 99.9% steady state within 20 days, while others e.g. 2,3,4,7,8-PnCDF will not exceed 50% of the steady state condition at the end of the three months dosing period. From the toxicological point of view these differences in steady state condition are undesirable, since the target tissue concentrations of the congeners are increasing differentially. As a consequence no clear cut relations between organ levels and toxic effects can be established. Therefore another experimental approach should be used, allowing a more precise comparison.

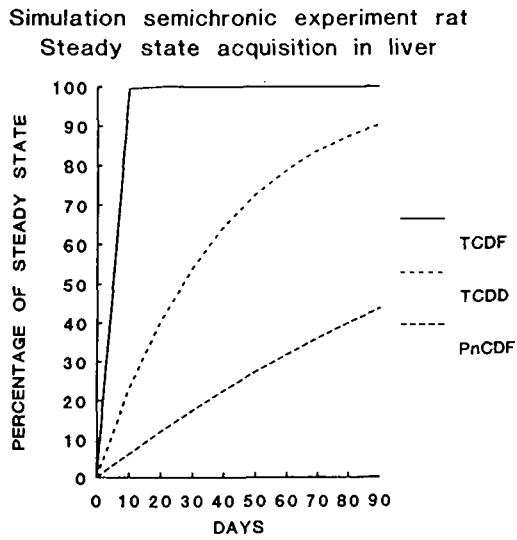

Fig. 1. Simulation of a steady state acquisition in three months study for 2,3,7,8-TCDF, 2,3,7,8-TCDD and 2,3,4,7,8-PnCDF in rats

In view of the nongenetic toxic action of these compounds a large extension of the experimental time period is considered to be unnecessary, when using experiments with low dose levels.

We propose such studies should include an initial "loading" period for about one week, yielding distinct predetermined organ/tissue levels, which should be maintained by daily dosage throughout the whole experimental period. An exact knowledge of kinetics of the compounds tested would certainly be a prerequisite in this approach.

THE ROLE OF KINETICS IN THE INTERACTIVE EFFECTS

Several groups have reported nonlinear interactive effects between PCDD/Fs and PCBs. These effects were antagonistic as well as synergistic (5,6,7), depending on the ratio as well as the species and parameter studied. However, irrespective of the type of interaction, the

effect is usually reported in a narrow concentration range. Such a "window" in which antagonistic or synergistic effects were reported for 2,3,7,8-TCDD and some PCBs was in the range 1 : 10^3 to 10^4. Outside of this ratio interactive effects were neglectible or not observed. Within the present TEQ concept nonlinear interactive effects can not be considered as its principle is based solely on additivity. In addition, the narrow concentration range, which is apparently a prerequisite for antagonism or synergism creates an additional complication for the human risk assessment.

Although interactive effects were reported with dosage ratios in the range 1 : 10^3 to 10^4, the ratio present in the target organs, e.g. thymus or liver, was not reported. In addition, interactive studies were done only with a single or few repetitive doses. Effects were usually observed a short time period after adminstration, e.g. 7 to 14 days.

Upon chronic administration of a combination of two compounds with distinctly different kinetics, we have to face a completely different situation. If we assume that interactions in the target organ require a similar ratio as for intake, it can easily be illustrated, that the ratio for such two congeners will change rapidly. This effect is illustrated in fig. 2, in which we have simulated liver tissue levels in rats during two years exposure to 2,3,7,8-TCDD and 2,4,5,2',4',5'-HxCB. For this simulation a daily dose of both 1 ng TCDD and 1000 ng HxCB was assumed, while published toxicokinetic parameters were applied (2,8). This semirealistic simulation clearly illustrates, that the original ratio is not maintained but changes rapidly. As a result the interactive effects, occuring only in distinct "windows", might be important only within a certain period.

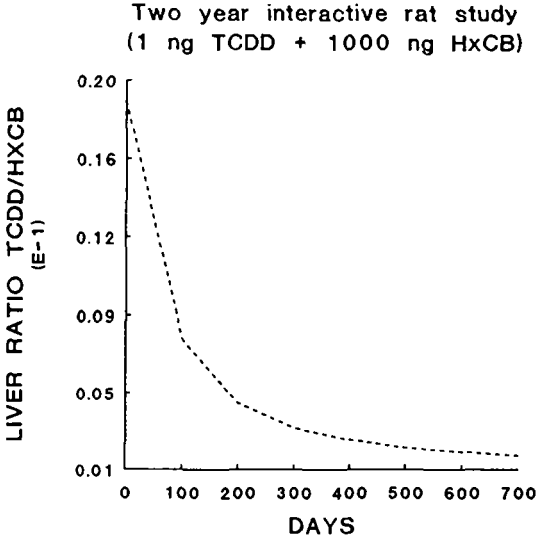

Fig. 2. Simulated chronic study with 2,3,7,8-TCDD and 2,4,5,2',4',5'-HxCB in rats.

In view of this considerations and the very limited data presently available, it is premature to incorporate such possible effects in the risk evaluations.

USING THE TEQ CONCEPT FOR HUMAN INTAKE

At present the risk assessment for human intake of these compounds is calculated by using TEQ values for the different PCDD and PCDF congeners. Calculations are based on additivity without making a discrimination regarding kinetics of the different congeners. This approach can partly be justified, as at present only the elimination rate for 2,3,7,8-TCDD in humans

is known (9). However, in most areas of the world human exposure to some other congeners, e.g. 2,3,4,7,8-PnCDF and OCDD, is quantitatively and toxicological far more important.
Animal experiments with other PCDD/Fs have shown, that kinetics and metabolism can differ substantially from that of 2,3,7,8-TCDD. At present there are no indications that similar differences might not occur in humans and we can assume that in humans similar differences in metabolism might be found depending on the chlorine substitution pattern in the molecule. When these differences in kinetics can be be included in future risk assessments, the toxicological significance of some congeners, e.g. 2,3,4,7,8-PnCDF, relative to 2,3,7,8-TCDD might drastically change. Unfortunately these phenomena can never be included in the present TEQ concept, as present values were derived from experiments in which kinetics and metabolism played only a minor role.

HOW TO IMPROVE THE TEQ CONCEPT IN THE FUTURE

As we have illustrated above the present TEQ concept suffers from a number of serious drawbacks, originating from the fact that in the present approach kinetics and metabolism are not at all considered. We believe that the present TEQ approach must gradually be replaced by a new system, in which biological response and kinetics should be the two fundamental pilars. TEQ values for biological responses can presently be obtained from in vitro assays or in vivo short term experiments. Kinetics can be included in this new approach by using computer modelling, calculating either target organ concentration or burden. The combination of the biological response factor and target organ concentration/burden will then be a more realistic approach for the human risk assessment. This dual approach is also a better approach to indicate possible nonlinear interactive effects between PCDD/Fs and PCBs. To realize this approach for risk assessment additional human data are necessary. Furthermore, animal data have to be re-evaluated to obtain toxicological, associated biochemical and toxicokinetic data relative to 2,3,7,8-TCDD.

LITERATURE

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