THE NEED FOR KINETIC CONSIDERATIONS IN THE ESTABLISHMENT OF TEF-VALUES

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Determination of toxic equivalency factors (TEFs)

Two different approaches can be (and have been) used to obtain data on the toxic potential of PCDD/PCDF-congeners relative to those of 2378-TCDD: In vitro model systems (e.g. enzyme induction) or chronic/subchronic animal feeding studies at the NOEL (classical toxicity study). Assessment of TEFs should be based preferably on feeding studies.
Presently, one has to assume an additive toxicity of the single PCCD/F congeners, when using the TEF concept for the estimation of the toxic potential of a mixture. In case of the PCDDs/PCDFs we have some evidence that antagonistic effects do not occur, however, such effects have been reported for mixtures of PCBs and 2378-TCDD.

Prerequisites for the use of TEFs for human risk assessment

a) The endpoint of a model system must correlate well with chronic toxicity regarding the NOEL. This is obviously not a problem in feeding studies.
b) The susceptibility of the target organs should be similar in the experimental animal an man. Usually this cannot be shown, but it is a basic assumption in toxicology.
c) Toxicokinetics of the compounds should be similar in man and experimental animals. This problem can be avoided when the evaluations are based on target organ concentrations.

The significance of kinetics

The whole-body half-life determines the steady state body burden in a chronic exposure situation. For example, the $t_{½}$ of 2378-TCDD in man is about 100 times that of rats. Thus, to obtain similar steady state body burdens humans would require only 1 % of the daily dose of rats.

The body distribution determines the target organ concentration in relation to body burden. As is shown later, rather large differences exist in the body distribution of these compounds between rat and man. The concentration ratio of 12378-PeCDD, for example, between adipose tissue and liver was reported to be about 1:13 in rats and 1:0.05 in humans. This would lead to an overestimation of the toxic hazard for man by a factor of 260, if adipose tissue levels would be the basis for comparisons. Therefore, target organ based comparisons are preferable.

Elimination kinetics of other isomers than 2378-TCDD

Elimination data are easily obtained from experimental animals. In rats, elimination half lives which have been reported so far lie between 2 days (2378-TCDF) and about 320 days (OCDD). Most likely, congeners with adjacent unsubstituted carbons are eliminated even faster than the 2378-TCDF [7].

Theoretically, an experimental approach in man would be possible if the congener is available at a high specific radioactivity (>10Ci/mMol). However, due to psychological reasons, the execution of such studies in humans is very limited. So far, only one such controlled study has been performed using 2378-TCDD [1].

Follow up of the blood fat levels after accidental intake of these compounds, leading to fat concentrations which are at least 10 times higher than the background levels, provides a possibility to determine their half-life in man.

Some indications could also be obtained from comparisons of the congener patterns and -concentrations in the human diet with those in human fat (Table 1).

Table 1: Average steady state concentrations of some of the most important PCDD/F congeners in human diet (milk fat) and human fat (breast milk), and their half-life (measured or calculated) in animals and man.

Congener	Fat concentration (ppt)		Ratio	Half-life	
	man [2]	animal [3]	man/animal	man (y)	rat (d)[4/5/6]
2378-TCDD	3.5	0.2	17	6 [1]	20
2378-TCDF	2.5	0.7	3.6	1.3*	2
12378-PeCDD	10	0.7	14.3	5*	30
23478-PeCDF	25	1.4	17.9	6.3*	64
123478-HxCDD	10	0.3	30	11*	110
1234678-HpCDD	50	2	25	9*	250
OCDD	335	10	33.5	12*	320

*Values are calculated on basis of the concentration ratio animal/human fat and the reported half-life of 6 y for 2378-TCDD.

The data in Table 1 show that in humans half-lifes of the individual congeners are generally much longer than in rats. For 2378-TCDF the ratio between man and rat is three times higher than for 2378-TCDD. This would lead to an underestimation of TCDF-toxicity if the evaluation is based on oral intake data of experimental animals. On the other hand, toxicity of HxCDD would be overestimated by a factor of about 3, and that of HpCDD by a factor of about 10.

Organ distribution of 2,3,7,8-substituted congeners

A drawback of the current TEF-based risk assessments, based on rat data is that it does not take into consideration organ distribution of PCDDs/Fs, which differs between rats and man. This became evident in recent studies reporting liver as well as adipose tissue levels of human samples.

Table 2: Liver to adipose tissue concentration ratios of 2,3,7,8-substituted congeners in man and rat. (Values are based on wet weight) [6/7/8].

Congener	Ratio Liver/Adipose tissue		Ratio
	Rat	Man	Rat/Man
2378-TCDD	3	0.3	10
PeCDD	13	0.05	260
HxCDD	30	0.1	300
HpCDD	60	0.5	120
OCDD	15	0.5	30
2378-TCDF	2	0.5	4
23478-PeCDF	40	0.2	200
12378-PeCDF	5	0.7	7
HxCDF	50	0.5	100
HpCDF	50	0.5	100
OCDF	50	0.5	100

Assuming that the concentrations in liver determine the toxicity, it becomes evident from these data (Table 2) that 2378-TCDF is underestimated by a factor of about 2 and the other congeners overestimated by a factor of up to 30 if comparisons are based on adipose tissue levels or body burden measured directly or calculated from the oral intake and the half life.

Conclusions

1. In the concept of TEFs toxicokinetic considerations must be introduced.
2. The important parameters are whole body half lives in experimental animals and man, and comparative data on organ distribution.
3. To avoid the interference of kinetic differences, comparative studies and evaluations should be based on target organ levels.
4. There is some justification for the use of TEFs for the evaluation of human PCDD/F intake from food sources.
5. The use of TEFs for other environmental material remains very doubtful, since the environmental behaviour of the congeners is not taken into account.

References

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