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Chemosphere, Vol.15, Nos.9-12, pp 1495-1502, 1986 0045-6535/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

BIOCONCENTRATION POTENTIAL (BCP) OF 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (2,3,7,8-TCDD) IN TERRESTRIAL ORGANISMS INCLUDING HUMANS

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ABSTRACT

The bioconcentration factors (BCFs) of 2,3,7,8-TCDD in adipose tissue of rats, beef cattle and monkeys have been calculated. The bioconcentration potential of TCDD in man was calculated by two indirect methods: 1) from daily intake of TCDD and its measured concentrations in adipose tissues and 2) from measured half-life and measured concentrations in body fat at steady state using a linear one compartment pharmacokinetic model.The BCFs in humans calculated by both methods are between 104 and 206, or 153, respectively.

1. INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), also known as "DIOXIN", "SEVESO POISON" or "TCDD", is not produced for commercial purposes and has no reported use other than a test chemical in research. However, it is formed during the thermolysis [1] of 2,4,5-trichlorophenol and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and has been found in fly ash and flue gases [2]. TCDD can also be formed by the combustion of chlorinated organic compounds, municipal and industrial waste.

Based on acute toxicity studies in several species of animals, 2,3,7,8-TCDD is the most toxic man-made chemical known. In spite of extensive investigations in recent years, the cause of liver injury and lethality, the mode of action and the mechanism of toxicity of TCDD are not known (Poland and Knutson, 1982)[3]. Recently, Rozman (1984)[4] proposed a hypothesis that interaction between thyroid hormones and brown adipose tissue are responsible for the many-thousand-fold species differences in TCDD toxicity.

Knowledge of human exposure to chemicals such as the PCDDs, polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs) and other persistent chlorinated aromatics, especially the highly toxic 2,3,7,8-tetrachloroisomers, is necessary to evaluate their risks. For this purpose, it is also useful to know the bioconcentration potential (BCP) of TCDD and to compare it with the BCP of other chemicals in humans.

TABLE 1

BIOCONCENTRATION FACTORS (BCFs) OF 2,3,7,8-TCDD IN LIVER AND FAT OF RATS, CATTLE AND MONKEYS (Kociba et al. [6], Kenaga [5], Jensen et al. [7] and Bowman et al. [8])

ANIMAL	DURATION OF FEEDING	CONCENTRATION IN			BCF_{Liver}	BCF_{Fat}
		DIET (ng/kg)	LIVER (ng/kg)	FAT (ng/kg)		
Rats	2 years	22	540	540	24.5	24.5
	2 years	210	5,100	1,700	24.3	8.1
	2 years	2,200	24,000	8,100	10.9	3.7
Beef Cattle	28 days	24	8.9	84	0.7	3.5
	499 days	24	-	594[a]	-	24.8[b]
Rhesus Monkey	4 years	25	-	600-1000	-	24-40

a) Calculated maximum TCDD residue at steady state ($t_{1/2}$ = 16.5 weeks)

b) Calculated BCF at steady state

2. BIOCONCENTRATION OF TCDD IN BIOTA, EXCLUDING HUMANS

Bioconcentration is the phenomenon that a chemical accumulates in organisms by direct contact with a surrounding medium through oral, percutaneous, or sometimes respiratory courses. In order to compare the bioconcentration potential (BCP) of different chemicals in organisms, the term bioconcentration factor (BCF) is used. Bioconcentration factor is the quotient of the test chemical concentration in the test organisms or tissues divided by the concentration in the test water (for aquatic organisms) or concentration in food (for terrestrial organisms), when the rate of uptake and clearance are equal, that means, when a steady-state or plateau value is reached.
TCDD has a very low water solubility (0.2-0.317 µg/l at 25°C) and a high lipophilicity. The experimentally determined n-octanol/water partition coefficient log K_{OW} varied between 6.145 and 6.19 (Kenaga, 1980)[5]. Because of these physico-chemical properties and its high stability against biotic and abiotic degradation, TCDD can be bioconcentrated in aquatic and terrestrial organisms including humans.
Some examples of bioconcentration factors of 2,3,7,8-TCDD in liver and fat of three different animal specics are given in Table 1.
From the calculated BCFs of TCDD in liver and adipose tissue of rats after a two-year study by Kociba et al. [6], presented in Table 1, it can be seen that the BCFs range from 10.9-24.5 in liver and from 3.7-24.5 in adipose tissue of rats fed 2,200 ng/kg, 210 ng/kg or 22 ng/kg TCDD in the diet. It is obvious that the BCF increased when the concentration in the diet decreased.
The bioconcentration of TCDD in fat and liver of cattle was investigated by Jensen et al. (1981) [7] feeding 24 ng TCDD/kg in the diet for 28 days. After 28 days the BCF of TCDD in liver was only 0.7 whereas the BCF in fat was 3.5. Using a linear one compartment pharmacokinetic model it was calculated that a steady-state in cattle would be reached in 499 days and the concentration in cattle fat would be 594 ng/kg. The calculated BCF of TCDD in fat after 499 days should then be 24.8. This value is in good agreement with the BCF of 24.5 calculated for rats which received 22 ng TCDD/kg in their diet for 2 years.
Recently Bowman et al. [8] studied the effects of TCDD in monkeys. After 4 years of chronic exposure to 25 ng TCDD/kg in their diet the TCDD concentration in subcutaneous and mysenteric fat ranged between 600-1000 ng/kg. The calculated BCFs in fat of monkeys ranged between 24 and 40.

3. METHODS FOR THE CALCULATION OF BCF OF TCDD IN HUMANS

Since it is unethical to test the bioconcentration potential of the highly toxic TCDD in long-term ingestion studies in humans, we used the following different indirect methods:

1) Calculation from daily intake and measured concentrations in adipose tissues and
2) Calculation from measured half-life and measured concentrations in bodyfat at steady-state using a linear one compartment pharmaco-kinetic model.

3.1 Assessment of BCF from daily intake

Presently it is not possible to determine the TCDD concentration in the total diet (cooked food), due to the very low concentrations. Therefore, it is only possible to assess the daily TCDD dose roughly. In accordance with Mackay et al. (1985) [9] and Hutzinger (1985) [10], it is our opinion that for TCDD food, especially fish, meat and dairy products, is the major route into humans. If the average Canadian's diet contains 6.5 g freshwater fish a day [10] and the TCDD concentration in freshwater fish would be between 5 and 10 ng/kg, as estimated by Ryan et al. (1983) [11], then the estimated intake would be 0.0325-0.065 ng/day. If the food intake is 0.63 kg/day [9], then the TCDD concentration in 1 kg food would be 0.052-0.103 ng/kg. If we use the TCDD concentration in human adipose tissue as measured by Ryan et al. [12] (10.7 ng/kg), then the calculated BCF would be between 104 and 206.
Hutzinger (1985) [10] calculated a daily intake of 0.13 ng TCDD/day and Graham et al. [13] a value of 0.05 to 0.2 ng TCDD/day. The agreement between these values and those calculated in this paper is satisfactory.

3.2 Assessment of BCF from a pharmacokinetic model

In mammals, 2,3,7,8-TCDD is readily absorbed through the gastrointestinal tract, and absorption through intact skin has also been reported. After absorption, 2,3,7,8-TCDD is distributed into tissues high in lipid content.
For the following calculations, the average concentration of 10.7 ng TCDD/kg adipose tissue in Canadians from the Great Lake area as measured by Ryan et al. [12], is used. The half-life ($T_{1/2}$) of TCDD in man was recently experimentally determined to be 5 years by Poiger [14]. The half-life of TCDD calculated by us is between 3.5 and 6.9 years and the average is in excellent agreement with the experimentally determined value of Poiger. Taking $T_{1/2}$ = 1825 days (5 years) and the fact that the lipid content of an average man of 70 kg is 11 kg, the amount of TCDD can be estimated according to the equation (1) for a linear one compartment open model:

$$m_d = \frac{m_{ss} \cdot \ln 2 \cdot t}{T_{1/2}} \qquad (1)$$

where m_d is the amount of TCDD absorbed during time t (which is one day in this case), m_{ss} is the amount of TCDD in the body fat at steady state, $T_{1/2}$ is the half-life in days = 1825 d and t is the interval at which doses are administered

(t = 1 day in this case).
The amount at steady-state in 11 kg fat would be 118 ng and the daily intake of TCDD is estimated to be

$$m_d = \frac{118 \cdot 0.693}{1825} = \underline{\underline{0.0448 \text{ ng TCDD}}} \qquad (2)$$

Assuming a consumption of 0.63 kg food per day [9], the concentration in food would be 0.07 ng TCDD/kg.
The bioconcentration factor (BCF) on a wet weight basis in human fat can be calculated by equation (3):

$$BCF = \frac{\text{Concentration in Fat (ng/kg)}}{\text{Concentration in Food (ng/kg)}} \qquad (3)$$

$$BCF = \frac{10.7}{0.07} = \underline{\underline{153}}$$

4.RESULTS AND DISCUSSION

2,3,7,8-TCDD has a low water solubility and a high n-octanol/water partition coefficient. Because of these properties and since it is metabolized very slowly, this chemical is bioconcentrated in terrestrial animals including humans. The biocentration factor (BCF) in lipids of rats ranges between 3.7 and 24.5, depending on the amount of daily intake (Table 1).It is obvious that the BCF of TCDD in rats increases when the concentration in the diet decreases (see Table 1). For this phenomenon two explanations can be given:

1) It is known that TCDD is a very effective inducer of cytochrome P-45o in rat liver. A single dose of 10 µg/kg body weight resulted in a three fold increase of total cytochrome P-450 (Thomas et al. 1982) [15]. It is therefore likely that at high doses of TCDD the enzymes in the liver are induced so that the chemical ist metabolized to hydrophilic compounds to a higher extent; thus, a relatively smaller amount is bioconcentrated.

2) It is also possible that high doses cannot be fully absorbed by the gastrointestinal tract, if it is an active transport process; hence the fraction of chemical which is taken up is lower for higher doses than for lower ones.

In beef cattle a BCF at steady-state was calculated to be 24.8. The BCF of TCDD in monkeys ranges between 24 and 40 after feeding 25 ng TCDD/kg in the diet.

The BCFs of TCDD in terrestrial organisms such as rats are in the same order of magnitude as calculated for p,p'-DDT, hexachlorobenzene and 2,2',4,4',6-pentachlorobiphenyl [16], which possess nearly the same lipophilicity as TCDD,

expressed as log K_{OW}.

The BCF value of TCDD in human adipose tissue, as calculated from the daily intake assessment, is between 104 and 206. The calculated BCF value from the pharmacokinetic model is 153 and is nearly the average of the value (i.e. 155) calculated from the daily intake.
The bioconcentration potential of a given chemical in humans depends on many factors, such as age, sex, health status, fat content of the individual and other factors, especially of physico-chemical properties of the chemical. Lipophilic chemicals, such as PCBs, DDT, HCB, which are metabolized to a low extent in mammals including humans, possess the highest bioconcentration factor in humans [17]. It is obvious that non-occupationally exposed humans eating much fish polluted by TCDD have a higher concentration of TCDD in their adipose tissue. However, since the concentration of TCDD in the total diet could not be determined thus far due to the very low concentration, it was only possible to assess the BCF roughly. It is evident that the kinetic behaviour of TCDD is somewhat more complex than that described by the linear one compartment open model. However, for most sets of data, this model is adequate. Furthermore, the calculated BCFs of TCDD in human adipose tissue are in the same order of magnitude as those calculated for PCBs, DDT and HCB which are also persistent against biotic degradation and have nearly the same high lipophilicity (n-octanol/water partition coefficients).

ACKNOWLEDGEMENTS

We are indepted to Dr. D. Bieniek, Dr. I. Gebefügi und Dr. K. Rozman for valuable discussions and for providing us with literature. We thank Prof. Dr. C. Rappe for a preprint of his publication and Dr. H. Poiger for data on the half-life of TCDD in man.

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