TCDD HALF-LIFE IN MAMMALS AND ITS DEPENDENCE ON BODY WEIGHT

Roberto Miniero, Elena De Felip, Fabiola Ferri, and Alessandro di Domenico

Istituto Superiore di Sanità, 00161 Rome, Italy

INTRODUCTION

Since the toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin has been shown to be due to the parent compound and not to its metabolites, TCDD metabolism and excretion are considered mainly a detoxification process [1]. In the characterization of TCDD toxicokinetics, several studies have assessed TCDD half-lives in different animals and tissues [1]. Interspecies differences in half-lives have been shown to be correlated with the body size of the organisms. In this regard, Walker [2] discussed the observation that the activity of an important group of enzymes, the microsomal monooxigenases, seemed to be correlated to organism taxonomy and body size.

In this paper, we report the results of an attempt to find a correlation between TCDD half-lives and body weight in mammals. Data dealing with TCDD toxicokinetic parameters in different animal species and in man found in the literature were reviewed. The main factors of variability affecting the toxicokinetics of this chemical are discussed.

METHODS

In this work, we tried to obtain an estimate of the correlation between TCDD half-lives in mammals and their weights under conditions of controlled exposure. Data were selected from published works on the basis of the animal species studied, their weight, exposure level, route of administration and TCDD whole body half-lives (Table 1). The studies on common laboratory species were done under controlled conditions, whereas the studies on humans and monkeys were less controlled. The presence of relative uncertainty factors in the experiment features are reported in the table remarks and in the text. In addition, where TCDD administration produced adverse effects (possibly reversible), this was also reported in the table. Mean weights and half-lives were log-transformed prior to inclusion in a linear regression analysis.

RESULTS AND DISCUSSION

The general trend of Figure 1 shows a good correlation between animal weight and TCDD half-lives in different animal species. Data appear to be grouped according to a number of factors, such as the species and strain and their relative susceptibility. Among the main factors influencing the dispersion of data, the characteristics of exposure and some experimental features like animal health and the number of assays relative to a single species, may have relevance. The correlation found may be the result of general features evenly distributed inside the organisms considered, such as: the low metabolization of TCDD and, consequently, its elimination mainly as parent compound; the overall processes of elimination, correlated to the amount of chemical in the body.

Table 1. Experimental data selected from the literature to analyze the dependence of TCDD half-life
on animal body weight.

SPECIES	WEIGHT[a] (g)	LEVEL OF EXPOSURE (μg/kg)	ROUTE OF EXPOSURE	HALF-LIFE[a] (days)	REMARKS	REFS
C57BL/6J Mice	30	32 (TCDD) + 0.032 (ITCDD)	ip + ip[b]	8.0	Pretreated mice	3
	30	0.032 (ITCDD)	ip	14.2	Naive mice	
C57BL/6J Mice	21	10	ip	11.0	—	4
DBA/2J Mice	21	10	ip	24.4	—	
B6D2F Mice	21	10	ip	12.6	—	
Golden S. Hamster	78	650	ip	11.95	—	5
	78	650	ip	10.82	—	
	78	650	po[c]	14.96	Body weight Loss and lethargy	
Hartley G. Pigs	480	0.56	ip	93.7	No sign of toxicity	6
Hartley G. Pigs	325	0.5	ip	30.2	No sign of toxicity	7
H/V Rat	316.6	5	ip	21.9	—	8
L-E Rat	258.3	5	ip	20.8	—	
Macaca mulatta	5250[d]	1	po	365	Unhealthy specimen	10
Humans	85000[e]	Unknown[f]	Unspecified	4124.5	—	11
Humans	85000[e]	Unknown[f]	Unspecified	2591.5	—	12
Human male	92000	1.14×10^{-3}	po	2120	No sign of toxicity	13

(a) Mean values.

(b) ip, intraperitoneal injection.

(c) po, per os.

(d) T.E. Rowell, 1984 [9].

(e) Presumed value.

(f) Prolonged.

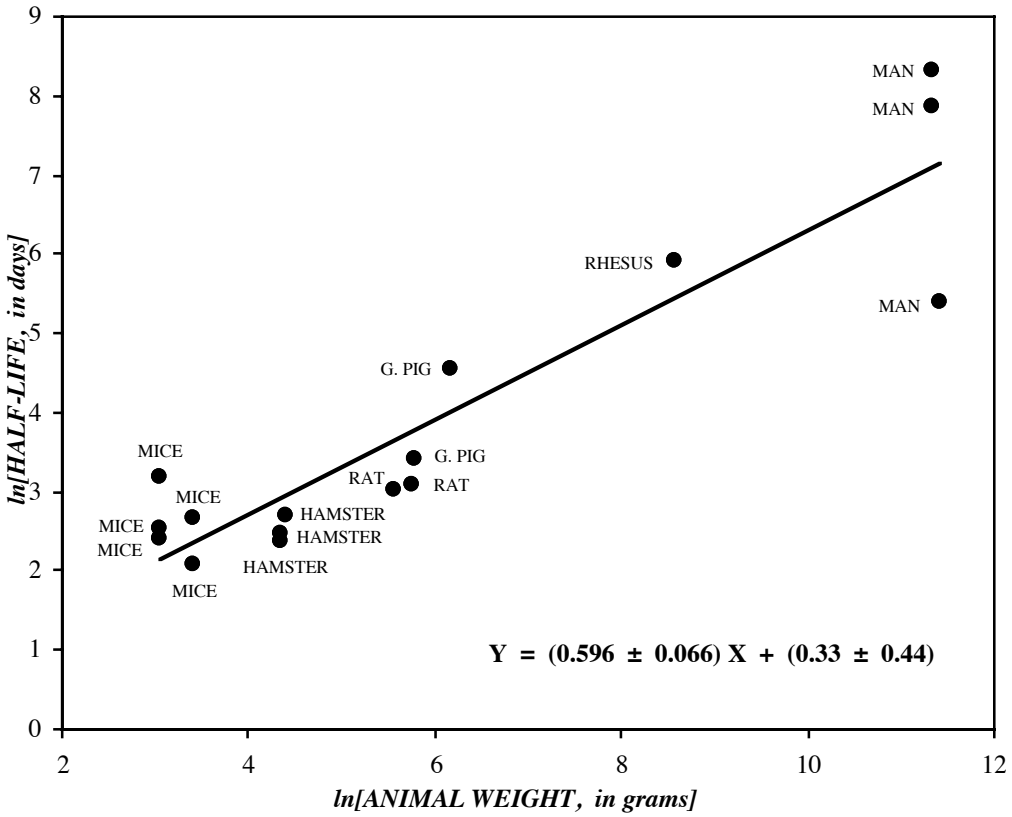

Figure 1. Trend of half-life as a function of animal body weight in different species. Both coordinates from Table 1 have been transformed to natural logarithms. The linear regression carried out appears to be highly significant (N = 16; R = 0.924, P_R < 0.001; $F(1.14)$ = 81.4, P_F < 0.001).

(these processes appear to be simplified due to the reduced rate of TCDD biotransformation and are normally assumed to follow first-order kinetics); the phylogenetic proximity of the organisms considered. However, several species- and strain-specific factors can markedly influence the chemical toxicokinetics, as briefly discussed hereafter.

Half-lives data on mice are characterized by a wide disribution along the Y axis. This response variability is a function of the inductive power of TCDD on microsomal TCDD-binding proteins [3], adipose tissues stores [4] and strain-specific differences. The importance of the role of TCDD-binding proteins in mice was analyzed by the application of a physiologically based pharmacokinetic model [3]. This model showed that differences in body distribution and elimination could be explained not only by differences in lipid contents, but also by the induction of binding proteins in mice liver [3]. The Ah-locus does not influence TCDD whole body excretion but can differentiate it in terms of route and rate between congenic sets of mice [14].

On the basis of the studies considered, after body weight normalization, the hamster results the animal model with the lowest TCDD half-life [5]. This could partly explain its low sensitivity to acute toxicity, as observed in other studies [1].

The half-lives of TCDD in rats and guinea pigs show a widespread distribution along the Y axis. Whole body clearance does not seem to be responsible of the higher susceptibility to TCDD toxicity of the rat strain Long Evans, in which the chemical half-life does not appear to differ from the half-life in the other resistant strain Han Wistar [8]. Liver and adipose tissue dose-dependent clearance rates have been found in the rat by some authors after a single dose exposure [15]; however, similar conclusions were not reached in a previous study [1], where animals were exposed chronically to two dose levels. Probably, the exposure rate and, consequently, the time course of tissue distribution are important factors in interpreting the differences observed.

The mean half-life value of TCDD in the guinea pig [6,7] does not appear to differ significantly from those reported for other rodents, as visible from the regression line. This fact is in agreement with the results obtained *in vitro* that prove a limited capability of the guinea pig to metabolize TCDD with respect to the rat [16].

The TCDD half-life determined in a specimen of *Macaca mulatta* [10] appears to be quite close to the regression line, slightly higher than predicted from the regression equation. The half-life derived from the cited study has to be considered cautiously because of the experimental conditions in which it was obtained (only one unhealthy specimen). Nevertheless, this value seems to be reliable considering the tissue-specific elimination data obtained on marmoset and rhesus [17,18] from, respectively, a single dose and long-term exposure.

A difference in tissue distribution between rodents and primates has been observed. The ratio between levels in adipose tissue and levels in liver is higher in primates than in rodents and can affect TCDD excretion rate, which is in general longer in primates than in rodents [1].

The persistence of TCDD in humans [13], obtained in controlled experimental conditions, appears to be considerably lower with respect to what would be expected based on our regression line. However, for Vietnam veterans in an unknown exposure situation, half-lives [11,12] appear to be higher than predicted from the regression equation. The above differences may be the result of the low number of experimental data obtained in controlled experimental condition and the two different exposure situations.

As already known, toxicokinetics cannot explain all interspecies differences observed in toxicity and toxicokinetic studies. Neverthless, the strong correlation found between TCDD half-life and animal body weight is interesting from a comparative point of view, in that it provides additional support for data extrapolation.

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