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Review

Risk assessment of dioxin contamination in human food

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Summary

Dioxins are highly toxic by-products of incineration processes and of production of chloro-organic chemicals. Accidental poisonings have occurred repeatedly. The main human exposure is via the dietary route. Species comparisons of toxic effects on the basis of ingested doses are not possible because of the highly differing toxicokinetics between humans and experimental animals. On the basis of internal doses or body burdens acute toxic and tumorigenic responses are observed at similar levels in humans and rats. PCB/PCDD/F contamination at levels which have been reported of marketed chicken meat and eggs in 1999 in Belgium may have increased body burdens by approximately 10%. However, it is estimated that a several hundred-fold higher uptake would be necessary to reach body burdens leading to overt toxicity in normal human subjects.

Keywords: Polychlorinated dibenzodioxins; Polychlorinated dibenzofurans; Polychlorinated biphenyls; TCDD; PCB; Diet; Pollution; Toxicity; Species comparisons

1. Introduction

Dioxins are a heterogeneous mixture of chlorinated dibenzo-*p*-dioxin and dibenzofuran (PCDD/F) congeners. Their ubiquitous occurrence, high chemical and metabolic persistence, and potent toxicity of some of the congeners make them a well recognized class of pollutants. Exposure of humans to dioxins occurs mainly (>95%) through contamination of food. The inhalatory route contributes only a negligible extent. However, accidental contamination of air in occupational settings and of animal feed have led to occasional poisonings of humans and livestock, respectively. The present risk assessment will briefly outline the major dioxin exposures and its toxicity, and finally characterize the health risk for humans associated with dietary uptake of a single highly contaminated meal.

2. Exposure and toxicokinetics of PCDD/F

The main sources of PCDD/F and PCB are production of chloro-organics and emissions of industrial and municipal incineration and pyrolysis processes (Fiedler, 1999). Transfer into human food occurs by particle-bound distribution on grass and other fodder plants and into the aquatic food chain. Ruminants accumulate these dioxin emissions (Riss et al., 1990). Cow's milk and milk products, bovine adipose tissue, hen's eggs and fish are the main contributors to human dioxin exposure in adults (Hallikainen and Vartiainen, 1997). The highest exposure in the human population occurs in infants via breast-feeding. However, unexplained differences have been observed between total 2,3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD) intake by infants and body burdens measured in early infant deaths. Abraham et al. (1996) have given indications that absorption in the infant gastrointestinal tract may be far less than in adults and recently LaKind and Filser (1999), as well as Kreuzer et al. (1997), have determined TCDD half-life in newborns to be 0.42 years only. These latter findings show that health risks for breast-fed newborns may be lower than previously anticipated.

There is great discrepancy in toxicokinetics between humans and rodents. The high metabolic stability and lipid solubility of dioxins leads to lifelong accumulation in humans. The half-life of TCDD (''Seveso Dioxin'') has been estimated in humans to 7 years (Poiger and Schlatter, 1986) and can be also derived from the steady decrease of dioxin concentrations (TE) from the lipid phase of human plasma (Wittsiepe et al., 1999) during the last decade in Western Germany. In rats, the half-life of TCDD is 4 weeks only (Van den Berg et al.,

Abbreviations: NDEA, *N*-nitrosodiethylamine; PCB, polychlorinated biphenyls; PCDD/F, polychlorinated dibenzo-*p*-dioxins and dibenzofurans; TCDD, 2,3,7,8-tetrachlordibenzo-*p*-dioxin; TE, toxicity equivalents; TEF, toxicity equivalent factors.

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1994). This difference makes it impossible to compare dioxin effects on the basis of external doses. Instead, internal or target organ concentrations are a more reliable basis for species comparisons as well as risk assessments. This will be discussed below.

3. Toxicity of PCDD/F

Not all chlorinated (brominated) PCCD/F have a high toxic potential, because only the 2,3,7,8 substituted congeners bind with high affinity to the (Dioxin-) Ah-receptor of mammalian cells. Receptor binding exerts toxic responses via expression of genes located downstream of the dioxin responsive element. TCDD is the most powerful of this class of congeners. Other compounds than PCDD/F that are also able to bind to the Ah-receptor possess primarily a similar molecular size as TCDD and are of planar conformation (Poland and Glover, 1977). These comprise all 2,3,7,8-substituted congeners of brominated and mixed chlorinated/brominated *p*-dibenzodioxin and dibenzofurans, several polychlorinated biphenyls (PCB). The differing binding affinities of the various PCDD/F and PCB congeners are accounted for by allocating toxicity equivalent factors (TEFs) in relation to TEF = 1 for TCDD, the most potent toxic congener (Van den Berg et al., 1998). Summarized external doses and internal (target) organ concentrations can be derived by multiplying analytically determined concentrations of the congeners with the respective TEFs which gives "toxicity equivalents" (TE). It should be mentioned here that several other compounds with molecular structural similarities to TCDD, like the polyaromatic hydrocarbon benzo[*a*]-pyrene, and the plant-derived food constituent indolo[2,3-*b*]carbazole, do also bind to the Ah-receptor (Gillner et al., 1985) and provoke toxicity similar to dioxins, for example induction of phase I and phase II enzymes, release of alanine aminotransferase from liver cells into plasma and severe neurological toxicity (Shertzer and Sainsbury, 1991).

Dioxin toxicity in humans became almost exclusively known through high occupational exposures or by chemical catastrophes. The following changes were most prominent after human intoxications (Sweeney et al., 1993): the occurrence of chloracne, increases in γ-glutamyltranspeptidase, increases in morning plasma glucose-, triglyceride- and cholesterol levels, further increases in luteinizing hormone and follicle stimulating hormone, but a decrease of testosterone levels, and finally a statistically increased incidence of diabetes (Ranch Hand Study; Sweeney et al., 2000).

The susceptibility of other species to the toxic effects of TCDD is variable and depends on adipose tissue to body mass ratio (Geyer et al., 1993). Induction of CYP enzymes is a very sensitive parameter in rodents and often used to determine TEFs (Safe, 1990).

In addition, multiple effects on endocrine and growth factor regulated processes have been reported (pleiotropic response; Safe, 1990). Studies with children exposed to dioxin-like PCBs prenatally and through mother's milk have indicated transient developmental neurological deficits in newborns and breast-fed infants (Koopman-Esseboom et al., 1994, 1996; Brouwer et al., 1995; Huisman et al., 1995; Weisglas-Kuperus et al., 1995). It is still the subject of research to assess whether normal intake of dioxins by breast-feeding may constitute a health risk in human development.

Enhancement and inhibition of tumor formation has been observed in experimental animals (Kociba et al., 1978). A summary of the results is given in Table 1. As can be seen, tumorigenesis was enhanced in female rats only in the liver, lung, nose and tongue, whereas the spontaneous tumor incidence which is high in female endocrine-dependent organs (pituitary, uterus, breast, pancreas and adrenals) was dose-dependently reduced. This gives an indication of the hormone-like interactions of TCDD in mammals. For further toxicological

Table 1
TCDD 2-year-carcinogenicity feeding study in rats (Kociba et al., 1978)

	Females				**Males**			
Dietary dose (ng/kg KG)	0	1	10	100	0	1	10	100
Animals per group	86	49	50	50	85	50	50	50
No. of rats with tumors								
Hepatocellular carcinoma	1	0	2	11	2	0	0	1
Strat. squamous carcinoma of the lung	0	0	1	4	0	0	0	1
Carcinoma of hard palate or nasal turbinates	0	0	1	4	0	0	0	4
Squamous carcinoma of the tongue	1	0	0	2	1	0	0	0
Pituitary adenoma	43	18	13	12	26	6	11	13
Uterus carcinoma	36	14	14	11				
Breast carcinoma	8	4	4	0	2	0	0	0
Pancreas carcinoma	3	3	1	0	12	3	3	3
Adrenal carcinoma	7	2	1	3	28	6	10	4
TCDD in adipose tissue of females and males	0	0.54	5,1	24	ng/kg			

risk assessments it was of great value that the authors had measured TCDD organ concentrations in liver and adipose tissue which will be used below. Studies on the genotoxic potential of TCDD have not revealed DNA binding or DNA mutations in bacterial and normal mammalian cells, nor has clastogenicity been detected (IARC, 1997). Further studies on the mechanism of TCDD carcinogenicity have established that it acts as a powerful tumor-promoting agent in the mouse skin model after initiation by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (Poland et al., 1982) and in the liver after initiation by *N*-nitrosodiethylamine, NDEA (Pitot et al., 1980; see Fig. 1). The tumor-promoting effect is evident by strong increases in foci volume after treatment with TCDD (dose-dependent) and with the standard liver tumor promoter phenobarbital (PB) and by an increase in tumor-bearing animals.

Slightly enhanced carcinogenic risks (1.5-fold) in occupationally exposed workers have been detected by epidemiological studies (Fingerhut et al., 1991). It remains to be proven whether changes observed in the regulation of organ growth and apoptosis in experimental animals

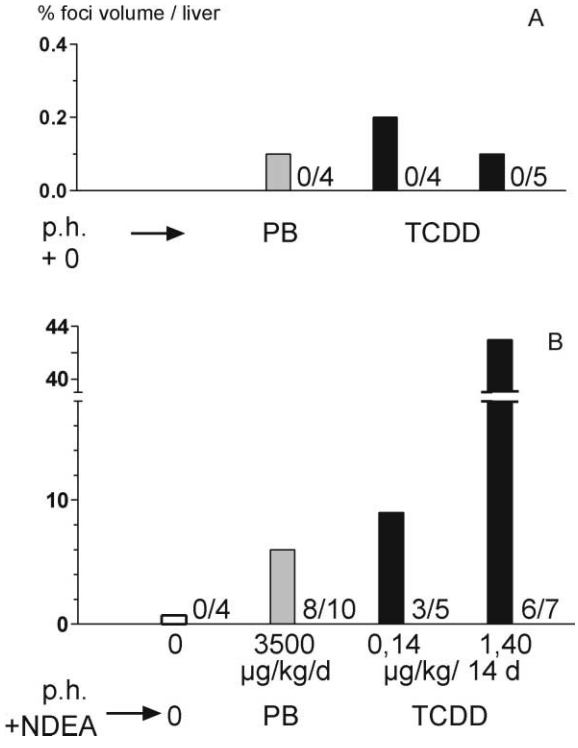

Fig. 1. Liver tumor promotion by TCDD (after Pitot et al., 1980). Female Charles River rats were partially hepatectomized (p.h.) and treated 13 h later with (A) saline, or (B) with an initiating dose of 10 mg/kg NDEA by intragastric intubation. After 28 weeks of treatment with Phenobarbital, Pb (0.05% in the diet) or TCDD (biweekly s.c. injections in corn oil) or vehicle alone (0), livers were examined by histomorphometry for development of altered hepatic foci. Hepatocarcinoma and hepatic nodules were diagnosed by histopathological criteria and the sum of both is given right to the bars as number of rats with tumors/number of rats examined.

may be responsible also for the human carcinogenesis by dioxins.

IARC (1997), has arrived at the overall evaluation: "TCDD is carcinogenic to humans". Consideration of the following mechanistic aspects of TCDD action were relevant to this judgement (McGregor et al., 1998): (i) TCDD is carcinogenic in multiple organs; (ii) TCDD effects are receptor mediated; (iii) the receptor functions similarly in animals and humans; (iv) the carcinogenic organ dose in animals and humans is in the same range.

Taken together, one can conclude that tumor promotion by TCDD is receptor mediated, and its hormone-like action in conjunction with lacking genotoxic potential allows to assume a threshold effect.

4. Human health risks by dietary dioxins

Human dietary intake of PCDD/F through different sources has been determined and daily doses of uptake have been calculated as shown in Table 2.

Populations consuming high amounts of fish in their diet have been shown to accumulate significantly higher levels of TE in their body fat than non- or moderate consumers; no clinical signs of health alterations were evident in the high fish consumption group (Svensson et al., 1991). So far, there are no reports to show that acute toxic responses occur in humans under normal dietary habits generating background dioxin body burdens. Also, no signs of chronic toxicity have been reported under these conditions. However, there are reports from accidentally highly exposed workers who had an increased incidence of infectious diseases (Zober et al., 1994), suggesting a weakened immune system. Also a higher incidence of infectious ear diseases were reported in Inuit children of Arctic Quebec after breast-feeding of babies whose mothers consumed high amounts of fish contaminated mainly with PCBs (Dewailly et al., 2000). Both these results are difficult to reconcile with one another and with other observations where no signs of immune system alterations could be found.

The question of whether a single episode of dietary intake of highly dioxin-contaminated food will pose a health hazard is discussed in this paper. Such events have occurred from time to time, as in the so-called "Yusho"; (1968 in Japan; Matsuzaka et al., 1969) and Yu-Cheng (1979 in Taiwan; Hsu et al. 1985) incidences, where contaminated rice oil had been consumed resulting in severe acute and chronic poisonings, and recently in the 1999 Belgium dioxin event (Bernard et al., 1999).

In 1999, chicken poisonings occurred in Belgium. Examination of animal feed revealed contamination with PCB and PCDD/F (at a ratio of about 22.000:1). Some of the poultry and eggs were marketed and eaten by consumers in Europe. Poultry meat and eggs contained high levels of PCBs and PCDD/F exceeding the

Table 2
Daily dose of dioxin uptake in Germany

pg TE/kg body weight	Cohort (years)	Year of examination
2.6	Children (2–5)	1994/95[a]
1.6	Children (1–3)	1998[a]
1.5	Adults	1988[b]
0.7–1.5	Adults	1994/95[a]
Approx. 0.5	Adults	1998[a]

[a] Wittsiepe et al. (1999).
[b] Fürst et al. (1990).

effectual tolerance limits for PCBs (0.2 μg/g fat) up to 250-fold.

A single high intake of dioxin equivalents (16 ng TE) might have occurred by consumption of a portion of contaminated chicken (12.5 ng TE) plus one egg (3.5 ng TE), assuming 100% absorption (Fürst and Schrenk, 1999). The dioxin body burden of an adult in Europe currently is in the range of 120–360 ng TE and would have been raised to 136–376 ng TE, an increase of 4–16%. Such change is considered to have no significance for human health (see below). Performing a similar calculation for a child carrying a basal body burden of 40–120 ng TE and taking up the same serving would sum up to a total body burden of 56–136 ng TE, which is equivalent to an increase of 13–40%. This load is considerably higher than that of an adult. However, it is highly unlikely that significant alterations in physiological responses might be induced, because in Seveso the most sensitive people developed chloracne only at TCDD concentrations of 800 ng/kg blood lipids (Mocarelli et al., 1991), which approximately equals a total body burden of 8500 ng. This body load is higher than in the above example by at least a factor of 60.

The body burdens mentioned above were derived from dioxin analysis in adipose tissue or from blood lipid phase of humans. A direct comparison of dioxin effects between species on the basis of the external dose is not possible because of the vastly differing toxicokinetics. However internal doses, such as organ concentrations, are more directly linked with toxic effects (receptor-mediated responses). The carcinogenic effects of TCDD in rats from the Kociba study (1978) are plotted on the left part of Fig. 2 at the respective adipose tissue concentration on the Y-axis. In humans (see right panel of Fig. 2) chloracne and increased tumorigenic risk occur at similar adipose tissue concentrations as in rats (see Fig. 2). When current background concentrations of dioxin toxicity equivalents (TE) in humans are plotted on the same scale it becomes obvious that the body burden would have to increase almost 150-fold in order to reach the lowest toxic concentrations found in sensitive individuals with chloracne in Seveso. For this, consumption of 300–500 portions, as given in the above example of the "Belgium chicken episode", would be required.

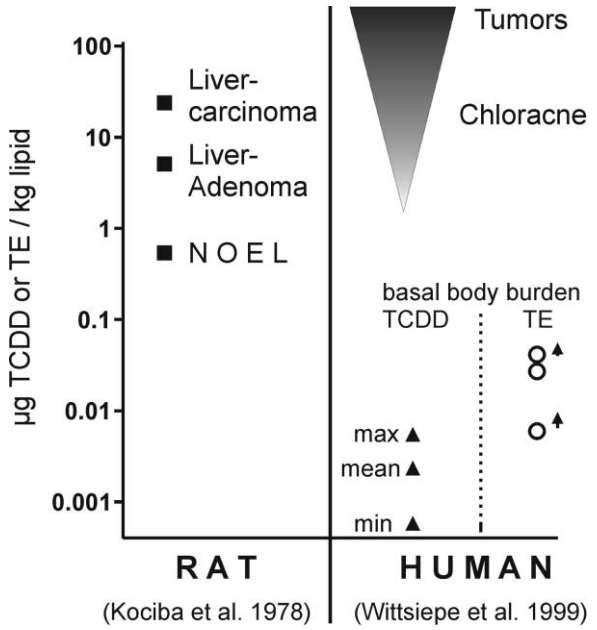

Fig. 2. Species comparison for dioxin body burden and effects based on adipose tissue concentrations. Rat data were taken from Kociba et al. (1976). NOEL is the no-observed-effect level of the 1 ng/kg dietary group; in the next higher dose group (10 ng/kg) adenoma, and in the highest dose group (100 ng/kg) carcinoma of the liver were detected. The large triangle indicates the range of plasma lipid concentrations at which individuals from the Seveso accident developed chloracne, and where in the upper range a carcinogenic risk might be noticeable. Current background concentrations are plotted by small triangles (TCDD) and by open circles (TE). The small arrows indicate the maximal possible increase by a single meal of contaminated chicken and egg as described in the example in the text.

5. Conclusions

The conclusions derived from the calculations and the comparative scheme in Fig. 2 are: (i) toxic symptoms are observed in rats and humans at similar endogenous dioxin concentrations; (ii) meals of high dioxin content will increase human body burdens; (iii) a single high intake by a normal adult individual does not pose any health risks.

In any case, repeated intake of dioxin-contaminated food must be avoided. Therefore, routine monitoring of animal and human foodstuffs for dioxins and dioxin-like PCBs by representative random sampling is mandatory.

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