Carcinogenicity Of TCDD In Animals And In Humans

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INTRODUCTION

The International Agency for Research on Cancer (IARC) first reviewed in 1977 the evidence of TCDD carcinogenicity in humans and animals (1). As a result TCDD was classified as carcinogenic in animals but it was decided that carcinogenicity in humans could not yet be reliably evaluated. Recent epidemiologic data have now established an association between high exposure to TCDD and several human cancers. Although debate continous, studies of the effects of dioxins in humans and experimental animals, including extensive research on mechanistic aspects of dioxin action, have provided increasing and more convincing evidence that dioxin is a human carcinogen.

CARCINOGENICITY IN EXPERIMENTAL ANIMALS

Seventeen long-term carcinogenicity studies reported between 1977 and 1988 have all positively demonstrated that TCDD is a potent animal carcinogen. These studies showed that TCDD is a transspecies (rat, mouse, hamster), transstrain (Sprague-Dawley and Osborne-Mendel rats, B6C3F1, Swiss-Webster, and B6C mice), transsex, multisite, complete carcinogen (2). It induces cancers in organs and tissues remote from the site of exposures at dose levels well below the maximum tolerated dose. A clearly noncarcinogenic exposure level could not be demonstrated with 1 ng/kg per day as the lowest tested dose.

Table 1 summarizes these carcinogenicity studies and includes information on routes and durations of exposure as well as tumor sites. Especially important are the Kociba (4) and the NTP studies (6,7) which are the most comprehensive and relevant for use in human risk-assessment. Mainly the tumor incidence in the female rat liver has been used in human cancer risk assessment but the male thyroid gland seems to be the most sensitive site for TCDD-mediated carcinogenicity. This is especially important since in recent epidemiological studies TCDD has been associated with cancer and other deseases of the thyroid gland in humans.

Limited data are available on the carcinogenicity of other dioxins or PCB's. One NTP carcinogenicity study tested a mixture of two isomers of hexachlorodibenzo-p-dioxin (1,2,3,6,7,8- and 1,2,3,7,8,9-HCDD) in rats and mice (10). This two-year study showed similar results at slightly higher doses than TCDD with liver being the more common target among species and sexes; the male thyroid gland was the more sensitive target. Other tested congeners acted as tumor promotors of hepatocarcinogenesis (11).

In summary TCDD and HCDD are potent multisite carcinogens in several species, specifically in mice and rats of both sexes. The sensitivity of the carcinogenic response varies between species, target organ and sex. Carcinogenic effects have been observed at doses over two orders of magnitude less than the maximum tolerated dose with the lowest observable effect at 1 ng/kg/day. Limited information is available on other congeners; however because higher chlorinated compounds (PCDDs and PCDFs) and dioxin-like PCB's bioaccumulate and exhibit toxic effects similar to those of TCDD, they must likewise be considered carcinogenic to animals and to humans.

Table 1 SUMMARY OF CARCINOGENICITY EXPERIMENTS OF TCDD

Sex, Strain, & Species	Routes, Exposures, & Durations	Cancer Results
Male Sprague-Dawley rats 10/group (Ref. 3)	Feed: 0.001 - 1000 ppb, 78 weeks exposure, + 17 weeks observation	Total tumors increased in all groups but 0.001 ppb
M & F Sprague-Dawley rats 86/controls & 50/exposure group (Ref. 4)	Feed: 21 - 2200 ppt [0.001-0.1 ug/kg/day], 2 years	M: tongue, nose, palate; F: Lung, liver, nose, palate
Male Swiss mice, 100 controls & 45/exposure group (Ref. 5)	Gavage: 0.007 - 7.0 ug/kg/week, 1 year exp, life-span observation	Liver tumors 0.7 ug group; none in 0.007; higher doses died
M & F Osborne-Mendel rats, 75/control & 50/exposure group (Ref. 6)	Gavage: 0.0014 - 0.071 ug/kg/day for 2 years	M: Thyroid, liver?? adrenal gland; F: Liver, skin, adrenal gland.
M & F B6C3F1 mice, 75/control & 50/exposure group (Ref. 6)	Gavage: M-0.0014 - 0.071 F-0.0057 - 0.29 ug/kg/day 2 years	M: Lung, liver F: Liver, thyroid gland skin, lymphoma
Swiss-Webster mice 45/control &30/exposure group (Ref. 7)	Dermal: 0.001-0.005 mg/application, 3times/week, 2 years	F: skin fibrosarcoma M: same??
M & F B6C3 mice 42-50/group	Gavage: 2.5-5.0 ugkg/week for 52 weeks, observed until 78 weeks	M: liver; F: liver
M & F B6C3 & B6C mice 89-106/group (Ref. 8)	intraperitoneal inj: 1-30 ug/kg/week for 5 weeks, observed until 78 weeks	All: lymphoma M & F B6C3: liver
M Syrian Golden hamsters, 10-24/group (Ref. 9)	Intraperitoneal injection: 100 ug/kg, 2-6 times, one/4 weeks; subcutaneous injection: 50-100ug/kg, 6 injections, one/4 weeks for 12-13 months	Both routes: facial skin, squamous cell carcinoma

notes: M = male; F = female; con = controls; exp = exposed; ug = micrograms; ?? = possibly

EPIDEMIOLOGICAL STUDIES IN HUMANS

Several epidemiological studies have been conducted on the adverse health effects associated with accidential or occupational exposures to phenoxyherbicides and chlorophenols contaminated with dioxins. Like animal carcinogenicity data, most epidemiology studies have focussed on exposures to TCDD, the most potent congener. Since more accurate measurements of TCDD tissue levels are now available, the observed health effects can be related to actual tissue burdens rather than estimated concentrations; and thus the question of dose response relationships can at least partially be addressed.

Four recently published studies, which include various exposure levels, provide evidence for increased cancer after high occupational (chemical workers in Germany and USA) or accidential (Seveso, Italy) exposure to TCDD. Table 2 summarizes some of the results of these cancer mortality studies. All studies show an increase in overall cancer mortality especially after high exposure and long latency, which might indicate a dose response relationship for the development of cancer. There is still some controversy on whether dioxins cause cancer and especially about their potency. Epidemiology studies on dioxins carcinogenicity are complicated by a number of factors. Mainly, exposure to dioxins usually occurs as a part of complex mixtures and background exposures to dioxins makes it difficult to determine control cancer rates. Also, there is

no pronounced site specificity for the carcinogenic action of TCDD. However, TCDD is a potent multisite carcinogen in rodents, and the lack of site specificity in human epidemiology studies is therefore consistent with animal studies.

TABLE 2: SUMMARY OF EPIDEMIOLOGICAL EVIDENCE OF TCDD CARCINOGENICITY

Location	Target sites	SMR [C.I.] [a]	Ref
Germany	Cancer mortality	201 [122-315; 90% CI]; 20+ yrs after expos	12
Germany	Cancer mortality	187-182[b], 20+ yrs employment	13
		161-187[b], employment before 1955	
		142-178[b], group with highest exposure	
	Total	124 [100-152] -139 [110-175][b]	
	Lung[c]	167 [109-244]; compared with gas workers	
	Hematopoietic[c]	265 [121-503]; compared with gas workers	
USA	Cancer mortality	115 [102-130]; Total cohort	14
		146 [121-176]; > 1 yr & > 20 yr latency	
	Connective & soft tissue	922 [190-2695]; > 1 yr & > 20 yr latency	
	Respiratory	142 [103-192] > 1 yr & > 20 yr latency	
	Lung	137 [98-198] [d]	
Italy	Hepatobililary	333 [130-810]; female Zone B	15
	Hematopoietic	210 [100-430]; male Zone B	
	Lymphoreticulosarcoma	570 [170-1900]; male Zone B	
	Multiple myeloma	530 [120-2260]; female Zone B	
	Myeloid leukemia	370 [90-1570][d]; female Zone B	
	Non-Hodgkin's lymphoma	200 [120-360]; male & female > 5yrs	
	Connective & soft tissue	280 [100-730]; male Zone R	
	Soft tissue sarcoma	350 [120-1040]; male & female > 5yrs	

[a]=standard mortality ratio: observed cases/expected cases times 100 [95% confidence interval].

[b]=first SMR of cohort versus national West Germany, second SMR of cohort versus worker cohort from gas supply company.

[c]=SMR compared to gas workers

[d]=CI includes 100, and thus p> 0.05

Since TCDD acts like a potent and persistent environmental hormone and growth dysregulator, non-cancer endpoints like immunological, reproductive, and developmental changes are being recognized as adverse outcomes following exposure to sufficient concentrations of dioxins. Important epidemiology studies published and/or under investigation should help to identify and further clarify specific risks resulting from dioxin exposure in terms of cancer as well as other adverse health effefcts.

The experimental, epidemiological, and mechanistic findings taken together lead to a strong association between exposure to TCDD and cancer in humans. The prudent course of action should therefore be to minimize all potential exposures to TCDD and other dioxins to the greatest extent possible.

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