

DISCUSSION

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- Q. How is coal volatilization process different from nuclear weapons detonation where refractories are on larger particles?
- A. Clearly, many elements display an increased concentration with decreasing particle size of coal fly ash. The size dependence appears to be due to a variety of factors including size distribution of mineral grains in the coal and the volatility, reactivity and stability of chemical or elemental forms that exist in coal. It is well established that those elements (or their oxides) which are volatilized at coal combustion temps are preferentially concentrated on fine fly ash particles, i.e. concentration of condensed volatilized forms is a surface related phenomenon. Decomposition reactions, e.g. carbonates or sulfates, may give rise to fine particle formation of relatively refractory elements. Such fine particles may agglomerate with larger particles, again giving rise to a surface related concentration enhancement. A similar argument pertains to mineral grains which may also give rise to fine particles of relatively pure materials. Chemical reactions may also give rise to volatile species from refractory compounds. For example, it has been suggested that silicon may be volatilized by reaction of silica with carbon resulting in formation of SiO. Subsequent nucleation processes may give rise to submicron agglomerates which deposit on surfaces of larger particles.

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Reversal of Immunologic and Toxicologic Effects of a Single Exposure of 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin in Mice

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ABSTRACT

A single dose of 10 $\mu\text{g/kg}$ of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in CD-1 mice produced signs of toxicity including microscopically detectable degenerative changes and increased weights in the liver, lymphoid depletion and decreased weights in thymus and alterations of various hematological parameters (decreased red blood cell count, lymphopenia and neutrophilia). This treatment also increased spontaneous transformation of lymphocytes in cell cultures prepared from spleens of treated mice. Transformation of these lymphocytes induced by mitogenic agents was reduced. These effects on lymphocyte transformation, apparent at 2 weeks post-administration, were not discernible at wk 4. By 8 wk post-administration, the wts of liver were approaching normal and the degenerative lesions observed microscopically were less severe; although thymic wts were still depressed, no lesions were microscopically discernible in this organ. At this time RBC counts were normal while mild lymphopenia and neutrophilia persisted. Transformation of lymphocytes, either spontaneous or mitogen induced, showed no deviation from that of control. These results indicate that in mice the toxicity of TCDD, including untoward immunologic effects, is reversible in a relatively short time.

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INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a highly toxic contaminant formed in the manufacture of trichlorophenol and in a number of other related compounds (4,12,19). It is one of the most toxic chemicals known (other than biotoxins). Studies on various toxic effects of TCDD have included teratologic (3), general toxicologic (6), pathologic (5) and other clinical effects (20). It is a potent inducer of hepatic microsomal enzymes (10) and causes induction of δ -aminolevulinic acid synthetase (9). A 13-wk oral feeding study in rats with different levels of TCDD and related toxicologic effects has been reported (7).

In addition, there have been implications that TCDD may adversely affect the immunological system. This chemical was shown to be particularly toxic to lymphoid organs, e.g. thymus (2). Gupta et al. (5) found that TCDD was toxic to the thymus of rats, mice and guinea pigs, despite some selectivity of other organs in these species. Vos et al. (17) reported the immunosuppressive effects of TCDD in rats and mice; subsequently Vos and Moore (16) suggested that the effects were primarily on cellular immune functions. Thigpen et al. (15) showed a decreased host sensitivity to bacterial but not to viral infections. In our recent studies (reported

separately) we have found a decreased responsiveness in mice and rabbits exposed to TCDD when their immune function is challenged with an antigen. Using a splenic cell culture system, however, an increased DNA synthesis in lymphocytes from animals exposed to TCDD was observed.

The objective of this study was to determine if the toxicologic effects, particularly the immunologic ones, are reversible with time. This report describes the time related effects in mice of a single exposure to TCDD for periods up to 8 wk.

MATERIALS AND METHODS

Male, CD-1 mice were obtained from Charles River (Wilmington, MA) and were acclimated for 1 wk. They were housed 2 per cage, provided free access to feed and water and kept in an environmentally controlled room with a 12 hr light/dark cycle. At the start of the experiment, the animals weighed approximately 28 g each.

The mice were divided into 2 groups; half were dosed with a solution of TCDD in corn oil (containing 5% acetone) at the rate of 10 μ g TCDD/kg and the other half were dosed with an equal volume of vehicle alone. Groups of 3-4 animals were sacrificed by decapitation at 2, 4 and 8 wk after treatment and blood was collected for total and differential cell counts and also to obtain serum. The liver, kidney, spleen and thymus were obtained and weighed. Spleen was used for lymphocyte cultures; other organs were placed in formalin fixative, processed routinely and examined for microscopic alterations.

Splenic cell cultures were conducted as described elsewhere (13). Suspension of cells obtained from these organs were cultured in triplicate with or without the presence of either phytohemagglutinin (PHA) or pokeweed mitogen (PWM) in micro-culture plates. After 48 hr of incubation in humidified air containing 5% CO₂, cultures were pulse labeled with 0.5 μ Ci of ³H-thymidine and incubation continued for additional 16 hr. The cells were harvested, washed and ³H activity counted in a liquid scintillation spectrometer. The counts were converted to disintegrations/min using a standard quench curve. After averaging the replicates for each culture, stimulation indices with both mitogens (dpm with a mitogen/dpm with no mitogen) were obtained and the animals in each treatment group averaged.

Serum immunoglobulins were estimated by electro-immunoassay using carbamylated rabbit anti-mouse immunoglobulin in an agarose gel system modified from Bjerrum *et al.* (1) by a procedure described previously (13).

The results are expressed as mean of observations with either standard deviation or standard error of the mean. Values in control and treatment groups were compared by t-test (14), using a prespecified p=.05 value.

RESULTS

None of the mice died due to treatment or showed any clinical effects of TCDD toxicity. Growth of treated animals was comparable to that of controls. Body wts, organ wts and organ/body wt ratios for selected organs are listed in Table I. A reduction in thymus/body ratio was observed in the group sacrificed 8 wk after TCDD exposure. The only other organ showing a change was liver; its absolute wt and the liver/body wt ratio increased consistently at all intervals, albeit a significant difference occurred only 4 wk after treatment. The increase in liver wt was nearly 18% at the 2 wk interval, rising to 26% 4 wk after exposure, but decreasing to only 11% by 8 wk after TCDD treatment.

Upon microscopic examination treatment related changes were observed in liver and thymus. The lesions were similar to those described elsewhere (13) and the incidence at different time intervals is summarized in Table II. Liver lesions included degeneration or necrotic changes at 2 and 4 wk after treatment whereas fibrosis with increased leukocytic infil-

TABLE 1. BODY AND ORGAN WEIGHTS OF MICE TREATED WITH A SINGLE ORAL DOSE OF TCDD (10 μ g/kg) AND SACRIFICED AT DIFFERENT INTERVALS^a

Time After Treatment (weeks)	Group	Body wt (g)	Organ Weights and Their Relation to Body Weight							
			Thymus		Spleen		Liver		Kidneys	
			(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)
2	Control ^b	33±4	0.06±0.01	0.17±0.03	0.11±0.06	0.33±0.16	1.90±0.29	5.68±0.38	0.53±0.08	1.60±0.10
	Treated	35±3	0.05±0.01	0.15±0.03	0.09±0.01	0.25±0.05	2.24±0.30	6.44±0.62	0.60±0.07	1.74±0.16
4	Control ^b	36±1	0.07±0.02	0.20±0.04	0.09±0.02	0.25±0.06	2.03±0.03	5.60±0.23	0.58±0.03	1.60±0.03
	Treated	39±4	0.07±0.02	0.18±0.04	0.12±0.05	0.31±0.08	2.55±0.29*	6.58±0.46*	0.64±0.09	1.63±0.07
8	Control ^b	40±3	0.08±0.01	0.19±0.02	0.10±0.05	0.24±0.10	2.05±0.24	5.07±0.31	0.60±0.07	1.49±0.11
	Treated ^b	42±5	0.05±0.02	0.11±0.03*	0.10±0.02	0.23±0.05	2.28±0.18	5.47±0.63	0.65±0.20	1.52±0.28

^aMean $\pm$ SD of 4 animals per group, except noted otherwise

^bOnly 3 animals per group

*Significant deviation from respective control at $p < .05$ (Dunnett's test)

tration was apparent at 8 wk. As seen in Table II, a progressive increase in the incidence of liver effects was observed when tissues were evaluated in a blind random fashion. The thymus effects included regression of cortical area, depletion of thymocytes and occasional pyknotic foci, but these were seen only in samples obtained at 4 wk after TCDD treatment. A gradual development of thymic changes that took nearly 4 wk, with a reversal of discernible effects by 8 wk, was evident from the results in Table II. No changes in kidney were observed.

TABLE II. INCIDENCE OF LESIONS IN LIVER AND THYMUS OF MALE MICE TREATED WITH A SINGLE DOSE (10 μ g/kg) OF TCDD AND SACRIFICED AFTER DIFFERENT INTERVALS^a

Duration After Exposure (Weeks)	Control		Treated	
	Liver ^b	Thymus	Liver ^c	Thymus ^d
2	0/3	1/3	3/4	0/4
4	2/3	1/3	4/4	2/4
8	2/3	0/3	3/3	0/3

^aSections were examined microscopically in blind random fashion. Kidney showed no remarkable change in any group. Numbers indicate incidence of lesions/total number of animals examined in that group.

^bLesions in control liver included vacuolization or slight degeneration of hepatic cells.

^cLiver in these groups generally showed slight to extensive diffuse degeneration or necrosis.

^dCortical atrophy with depletion of thymocytes seen in thymus of animals sacrificed 4 weeks after treatment.

Hematological examination (Table III) revealed a significant reduction in the total number of erythrocytes at the 4 wk interval. This change was not noted at 8 wk post-exposure. Total leukocyte counts showed no change at any of the sampling periods. A consistent increase in the number of segmented neutrophils and a corresponding decrease in the number of lymphocytes was observed at all intervals.

Splenic lymphocyte cultures at different time intervals showed that at 2 and 4 wk after TCDD treatment there was a marked increase in DNA synthesis in unstimulated cultures. Although the extent of average increase was similar at these 2 periods, there was greater variation at 4 wk, making the difference statistically non-significant (Table IV). At 8 wk, uptake of tritium was similar for both control and treated groups. When these cultures were supplemented with either PHA or PWM, the resultant mitogen-induced stimulation was decreased considerably at 2 and 4 wk after treatment with TCDD, but control and treated groups were similar in this respect at 8 wk post-treatment. Estimation of serum-immunoglobulins indicated that a single exposure of 10 μ g/kg TCDD did not produce any marked change in this parameter at either period of sample collection (Table V).

DISCUSSION

Results indicate that TCDD in a single dose of 10 μ g/kg is toxic to mice and the toxicity is evident by decreased thymus wt, increased liver wt, alterations in hematological parameters and histopathological lesions, primarily in liver. In general these toxic effects seem to be reversible and the reversal may be evident as early as 8 wk after exposure to TCDD.

TABLE III. SELECTED HEMATOLOGICAL PARAMETERS IN TCDD EXPOSED MICE

Weeks after TCDD Exposure	Group	RBC $\times 10^{-6}/\text{cmm}$	WBC $\times 10^{-3}/\text{cmm}$	Percent incidence of		
				Neutrophils	Lymphocytes	Monocytes
2	Control	8.02 $\pm$ 1.11	2.7 $\pm$ 1.1	15 $\pm$ 7 (405) ^a	83 $\pm$ 7 (2241)	2 $\pm$ 2
	Treated	8.21 $\pm$ 0.55	2.9 $\pm$ 0.7	25 $\pm$ 4* (725)	72 $\pm$ 3* (2088)	2 $\pm$ 3
4	Control	8.75 $\pm$ 0.40	1.7 $\pm$ 0.4	17 $\pm$ 3 (289)	80 $\pm$ 1 (1360)	1 $\pm$ 1
	Treated	7.94 $\pm$ 0.21*	2.2 $\pm$ 1.3	41 $\pm$ 18* (902)	56 $\pm$ 18* (1232)	2 $\pm$ 1
8	Control	8.75 $\pm$ 0.56	2.0 $\pm$ 0.2	21 $\pm$ 7 (420)	75 $\pm$ 3 (1500)	3 $\pm$ 2
	Treated	8.08 $\pm$ 0.38	2.1 $\pm$ 0.9	55 $\pm$ 22* (1155)	41 $\pm$ 22* (861)	3 $\pm$ 1

*Significantly different from respective control group values in parentheses indicate number per cmm

TABLE IV. THYMIDINE UPTAKE BY SPLENIC LYMPHOCYTES AND MITOGEN STIMULATION INDICES IN MICE AFTER SINGLE ORAL DOSE OF 10 $\mu\text{g}/\text{kg}$ TCDD^a

Time After Exposure	Group	DPM/ 10^6 Cells Without Mitogen	Stimulation Index ^b With	
			PHA	PWM
2 weeks	Control	37,522 $\pm$ 12,965	1.99 $\pm$ 0.81	12.59 $\pm$ 10.43
	TCDD Treated	339,234 $\pm$ 119,811*	0.51 $\pm$ 0.32	1.08 $\pm$ 0.45
4 weeks	Control	30,794 $\pm$ 7,638	11.06 $\pm$ 2.58	14.11 $\pm$ 1.78
	TCDD Treated	268,569 $\pm$ 242,920	5.29 $\pm$ 2.21	7.06 $\pm$ 2.58*
8 weeks	Control	22,860 $\pm$ 12,603	1.15 $\pm$ 0.51	4.63 $\pm$ 0.79
	TCDD Treated	20,386 $\pm$ 15,243	1.83 $\pm$ 0.47	3.85 $\pm$ 1.51

^aMean $\pm$ SE of 3-4 animals per group

^bStimulation index = dpm in the presence of mitogen divided by dpm without mitogen

*Significant difference ($p < .05$) from respective control group

TABLE V. SERUM IMMUNOGLOBULINS IN MICE AFTER
A SINGLE DOSE OF 10 μ g/kg TCDD

Group	Serum Ig Levels ^a After		
	2 weeks	4 weeks	8 weeks
Control	1.37 $\pm$ 0.23	1.13 $\pm$ 0.10	1.24 $\pm$ 0.07
Treated	1.13 $\pm$ 0.19	1.20 $\pm$ 0.13	1.09 $\pm$ 0.16

^aValues are ratios of total serum immunoglobulin to that of a pooled mouse serum sample. Mean $\pm$ SE of 3-4 observations per group.

The severity of pathologic changes in the liver was most pronounced at 4 wk after treatment. At 8 wk liver lesions were more of a chronic type, i.e. fibrosis. The incidence of thymic changes was highest at 4 wk post treatment and even though a decreased thymus wt was noted after 8 wk, histologic changes were not observed at this interval. In another study where mice were given repeated weekly doses of different amounts of TCDD no effects on the thymus after 8 wk were noted (13). These findings indicate that the toxic effects of TCDD to this organ are not only reversible but even with continued exposure there is an adaptation.

The single dose oral LD50 of TCDD in male mice is reported to be 114 μ g/kg (18). Following a single administration more than half the total body burden for TCDD is accounted for in the liver in a sensitive strain of mouse (9). According to the data presented by these authors, the concentration of TCDD from C57BL/6J mice liver disappeared at a half-life rate of approximately one wk. This value is considerably smaller than the whole body half-life value obtained in rats (8,11). In view of these observations a major fraction of TCDD in the liver of mouse may have been eliminated in 8 wk, while it may be more persistent in other species, e.g. rats. If this interpretation is correct, the effects of TCDD in liver and other organs will disappear in this time interval.

A marked effect of TCDD exposure was seen on the splenic lymphocyte transformation in cultures. A single dose of TCDD caused a considerable increase in spontaneous blast formation in splenic cultures obtained from treated animals. This finding was also observed when exposure of TCDD was repeated once a week for 8 wk (13). Although the implication of this finding is not clear, nor is its mechanism understood currently, this effect is most striking 2 wk after administration of 10 μ g TCDD/kg. After 4 wk the effect persisted, although there was great individual variation in these parameters. In another study (data not reported) we exposed adult (4-5 mo old) mice to the same dose of TCDD (vs. growing mice in present report) and a similar, although less extensive, effect was seen when the spleens were cultured 2 wk after treatment. Another important consideration of this increase in spontaneous lymphocyte transformation is decreased responsiveness to mitogenic agents giving rise to smaller stimulation indices in treated animals. This is indicative of decreased responsiveness of the immune system to antigenic stimulation, also confirmed in another study (13). The major finding of this study is that both spontaneous blast formation and mitogen induced stimulation return to normal in 8 wk after TCDD exposure. This further supports the argument of the reversal of toxic effects of TCDD in mice within a relatively short time.

It is difficult at present to extend these findings to an accidental human exposure to TCDD since it is well known that considerable species variation occurs in response to this toxic chemical. But the differences in physiological disposition would alter the rate at which the body is cleared of the chemical and if a sublethal exposure occurs, the effects probably can be reversed with time. The immunologic effects were not last-

ing whereas the hepatic effects persisted. Perhaps accumulation of TCDD in liver may be considered a defensive mechanism, at least insofar as the immunologic alterations are concerned.

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V ENVIRONMENTAL POLLUTION

Dioxin and Soft Tissue Sarcomas

There are two kinds of data involved in the current debate about the link between soft tissue sarcomas and exposure to 2,3,7,8 TCDD ("dioxin"). The first kind might be called "after the fact" data. They consist of several soft tissue sarcomas that turned up in three studies, two at Monsanto and one at Dow, and were noticed after the fact by investigators at NIOSH. These investigators then looked for other soft tissue sarcomas and found some at two Monsanto plants. Whether there are four or five or seven such cancers depends on how one defines exposure, but in any case these are reported to be in excess on the basis of conventional statistical calculations.

These calculations are suspect because they were made after the fact. To see this, notice that there have been some 7000 workers with potential exposure to dioxin nationwide in some eight plants (NIOSH data). NIOSH observed cases coming from two plants, and calculated "excesses" based on the populations of those plants. What they should have done, and are now in the process of doing, is to follow up the whole 7000 workers and to relate whatever number of soft tissue sarcomas are found to this population of 7000. It may be that this process will turn up a true excess, but until it is done the significance of the currently known soft tissue sarcomas cannot be evaluated.

The second kind of evidence consists of a series of epidemiologic studies directed specifically toward soft tissue sarcomas. These began when a Swedish group did two studies comparing cases of soft tissue sarcomas to matched controls who did not have cancer [1,2]. Both groups, or their next of kin where necessary, were interviewed by telephone about past chemical exposures. There was more exposure to phenoxy herbicides, which could have dioxin as a contaminant, in the cases than in the controls. Exposure was estimated to be associated with a six-fold increase in risk.

The studies were criticized by other investigators [3,4]. In brief, the method of obtaining exposure information was prone to bias, and the duration of exposure of the cases was suspiciously short. Other technical problems also surfaced, and other investigators attempted to confirm or refute the findings through independent studies with different designs.

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Two general mortality studies of Swedish forestry workers and railway pesticide sprayers showed no soft tissue sarcomas [5,6]. A similar study of Finnish herbicide sprayers also showed no soft

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tissue sarcomas [7]. Finally, a New Zealand study, similar in design to the Swedish studies but with more attention paid to controlling possible bias, did not confirm the Swedish findings [4,8].

In summary, we have a small number of soft tissue sarcomas among two groups of workers involved in the production of 2,4,5 T. Their significance cannot be evaluated. We also have six epidemiologic studies, two of which show a relationship between soft tissue sarcomas and dioxin and four of which do not. The only thing that seems clear is that the NIOSH nationwide study of dioxin exposed workers should certainly go forward, and that the National Cancer Institute should be encouraged to conduct a study based on the Swedish design in order to further clarify the situation.

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H. C. GODT, JR.

JUL 29 1983

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George!

As requested. Don't
forget, I want copies
of your slides from
the Dioxin symposium.

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