

LESSONS LEARNED FROM THE DIOXIN PROBLEM

PRESENTATION

RAMS

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I spent a great deal of time over the last two years worrying and learning about dioxins. The Agent Orange controversy, the possible reproductive effects of 2,4,5,T spraying, and the finding of environmental contamination in Missouri has kept the dioxin problem before the public eye. It undoubtedly was the basis for the Council of Scientific Affairs of the AMA in its report on the health effects of Agent Orange and dioxin contaminants.

A great deal has been written about dioxin and several excellent comprehensive reviews have been assembled by the VA, the EPA, and the NRC of Canada. In addition, our plant population at Nitro, West Virginia has been the subject of two intensive clinical studies - one by Ray Suskind at the University of Cincinnati and the other by Marian Moses and Mount Sinai staff. This year a further study of this group was done by the Department of Medicine and others at the West Virginia University Medical School.

First, I will give you a summary of what is known about this subject based on my reading as well as the experience I just cited. Then, I will give you what I believe are the lessons learned from this dioxin problem.

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I hope that it will be apparent that the lessons of surveillance of dioxin are applicable, at least in part to all occupational medicine.

It was early in the production of chlorophenols and especially 2,4,5,T in the early '50s that a chloracne problem was recognized. Though it is stated that chloracne is common, most physicians have not seen it or are not aware that they have seen it. A picture of a man with extensive papular lesions and cysts involving every follicle on the face is not typical - it is much more seen as a few comedones along the malar eminence.

A series of accidents in the '50s and '60s in the production of 2,4,5,T resulted in explosive release of trichlorophenol contaminated with dioxin. The workers in the cleanup of these plants were exposed to more dioxin than is the usual case. It was about 1957, that it was first recognized that a contaminant, 2,3,7,8 tetrochlorodibenzo dioxin was the cause of this chloracne.

As a result of the isolation of this chemical and the many cases of chloracne that interest in the toxicology of dioxin grew.

A dioxin I will be discussing will be 2,3,7,8 tetrochlorodibenzo dioxin. There are seventy-five isomers of the polychlorinated dibenzo dioxins depending on the number of chlorines and their location on the molecule.

Of these seventy-five isomers of chlorinated dibenzo dioxins, only a relatively few had been studied toxicologically, but they do vary greatly in their toxicity. Using LD₅₀ data for the guinea pig, the most toxic was the 2,3,7,8 isomer and the least toxic was the 2,8 isomer. There was more than a hundred thousand fold difference in toxicity between these two dioxins. Such data clearly state that all dioxins are not equally toxic, but even the least toxic would be considered moderately toxic. The data do also point out the difference in the toxicity of all of the dioxins for the mouse and the guinea pig.

The next transparency demonstrates more clearly the great difference in toxicity of the dioxins for different species. The literature usually compares the toxicity in the guinea pig and the hamster and it shows that the guinea pig is five thousand times more sensitive to 2,3,7,8 TCDD than is the hamster. For the guinea pig, the lethal dose is about one microgram making this dioxin one of the most toxic of chemicals. Looking at these species comparisons, most have questioned where man would fit on this list; though many would say we must conservatively consider man as sensitive as the guinea pig, those who have studied the acute toxicity of dioxins think that man probably falls in the range of the monkey to the dog, suggesting that the single dose LD₅₀ would be in the range of 100-300 µ/kg or 7-20 µg.

The cause of death from such overexposure is not at all understood. The death is slow, taking several weeks. It is accompanied by marked weight loss (25-35% of the body weight), and thymic atrophy is a constant

finding. It is thought that the cause of death looks most like starvation. The liver is damaged in the rat, rabbit, mouse, and dog, but not in the monkey, guinea pig, or the hamster. In the monkey, there is an effect on the bone marrow and epithelial tissues, but still the ultimate target organ is unknown.

In subchronic studies of thirteen weeks in a rat, .1 $\mu\text{g}/\text{kg}/\text{day}$ was toxic and 0.01 μg or 10 $\text{ng}/\text{kg}/\text{day}$ was a no effect dose. The clinical effects include decreased cholesterol, blood glucose, total serum protein and albumin, increased BUN, SGOT, aldolase, GGT, porphyria, and enzyme induction. The pathologic findings include alveolar hyperplasia, interstitial inflammation, and pulmonary fibrosis. Decreased spermatogenesis and immuno suppression is also noted.

Lifetime feeding studies with the 2,3,7,8 isomer in rats have produced liver cancers and squamous cell cancer of the lung in the females, and tumors of the adrenals in the males. 0.01 $\mu\text{g}/\text{kg}/\text{day}$ produce these lesions and 0.001 μg or 1 $\text{ng}/\text{kg}/\text{day}$ was a no effect level. Other studies have shown that 2,3,7,8 isomer is also carcinogenic in a mouse.

To round out the picture, .01 $\mu\text{g}/\text{kg}/\text{day}$ was fetotoxic in a rat and .001 μg was the no effect dose. In the mouse, 2,3,7,8 TCDD is a teratogen at 1 $\mu\text{g}/\text{kg}$ but not at .1 μg , producing cleft palates and dilated renal pelvises. Interestingly, apparently TCDD is not mutagenic.

The salient features of these experimental studies are as follows:

- 1) 2,3,7,8 TCDD is extremely toxic; a dose of 1 μg can be fatal in the guinea pig.
- 2) It affects most organ systems in the poisoned animal.
- 3) It is carcinogenic and a reproductive hazard at one one-hundredth of the LD_{50} or at 10 ng/kg/day.
- 4) A safe dose for exposure to this isomer, based on one of the models used in risk assessments is 30 femto grams/kg/day.

With this brief look at the experimental data, let's look at human experience. 2,4,5,T, 2,4,5,Trichloro phenoxy acetic acid, was first produced in 1944 and was used as a herbicide in increasing amounts until 1969 and was used without apparent incident. In the production of 2,4,5,T, there have been a number of workplace incidents which resulted in exposure by the workers to reaction products. Many of these workers developed chloracne, and in addition, some experienced liver effects, neurologic abnormalities, fatigue, and in several occasions, porphyria. Without such gross exposures, lesser degrees of chloracne occurred without other apparent effects. Study of these workers, years after exposure, showed persistent chloracne in some but without other observable effects.

Nevertheless, there is expressed concern that some of these workers may have had effects other than chloracne, but no surveillance survey has been done to document whether there are other effects which can occur in the absence of chloracne.

Because of the carcinogenic potential of 2,3,7,8 TCDD, a number of mortality studies have been done and with different findings. The Monsanto study of the largest population, after thirty years, demonstrated no excess cancer. The finding of excess soft tissue sarcomas in Sweden has not been confirmed in other studies.

When this human experience, and it is considerable, is considered in light of the experimental data, the following questions are often raised:

- 1) Is the chloracne a manifestation of dermal exposure or of systemic intoxication? It is recognized that 10 to 100 µg of dioxin on a rabbit ear produces a chloracne-like response. The Yusho incident where many Japanese ingested PCBs and dibenzofurans, developed a similar skin response to chloracne but not identical to it.
- 2) Is chloracne always present when other manifestations of the intoxication are seen?
- 3) Cancer in man from the exposure to dioxin has not been ruled out.

With this overview of the toxicity and hazards of dioxin, I would like to tell you how Monsanto got involved in this controversy. Dr. Suskind, who examined the chloracne cases in the Monsanto Nitro episode in 1949, asked Monsanto to do a mortality study on those episode workers. He thought such information would be meaningful to the Seveso exposed population. This was done. He also requested Monsanto to do a morbidity study and this was done in 1979. Dr. Marion Moses of Mt. Sinai did a similar study

in 1979 at the request of the local union. Both of these studies were published in 1984. Then in 1980, Monsanto was sued by 170 workers at the Nitro plant and in 1979, a spill of chlorophenol in a train accident in Sturgeon, MO resulted in three lawsuits, one by the railroad workers involved in the cleanup, another by the families of the railroaders, and a third by the town inhabitants, all alleging dioxin effects. The other lawsuit related to dioxin was the Agent Orange suit filed by veterans which was settled in 1984.

Since Monsanto had stopped production of 2,4,5,T in 1969 - before I joined Monsanto - I thought Agent Orange production had only historical importance for me. The request of Suskind to the studies of both mortality and morbidity were for the reassurance of the Seveso exposed population was reasonable. It is easy for me to develop a list of lessons learned from the dioxin problem since I do not have to defend Monsanto efforts and since I am looking back at what should or could have been done. My list of recommendations will be given in a chronological order. I must admit these recommendations are explored by the litigation we are facing, but I've told you, I thought we had no dioxin problem.

- 1) To begin, when an incident occurs, such as the appearance of chloracne in a workforce, the effects and any associated effects should be documented as soon as possible - that is not easy to do in many cases, but clinical consultants can and should be used to provide reassurance that you are doing the best possible. This was as true back in 1950 as it is today -

several Nitro cases were sent to the University of Cincinnati for workup at that time. Today, we are not permitted to be general practitioners.

- 2) Next, every effort must be made to prevent further cases, and we must document our efforts to do this. I don't believe we are permitted to have this same problem persisting for months and years. This is a defensive measure because of potential liability and, today, I don't believe we are permitted to do other than this.
- 3) As information is developed regarding effects and possible effects, then a surveillance procedure must be developed and implemented when possible. This is also difficult to do. This involves adding new procedures that are new and untested. A new procedure probably should not be added if it is not understood clinically, even by the experts.
- 4) When the study has reached this stage, consider an external morbidity study - the studies of Suskind and Moses have been of inestimable value. They brought fresh viewpoints to the surveillance and their findings are considered to without bias.
- 5) Concurrent with the development of all the clinical data to this point, a method of monitoring of exposure should be developed if at all possible. Though dioxin analyses are a part of the new chlorinated hydrocarbon analytical procedures,

they would have been a tremendous value in our understanding of the magnitude exposure when chloracne was seen. A great deal of controversy today concerns the exposure that Seveso, in Missouri, and in our plants today, as compared to those and the explosions of the past. Dr. Kamer at Pittsburgh told me many years ago, we can't waste these exposures - we must learn all we can from them. Such data would be useful and a comfort to our workers, to the regulators, and the public. In addition, a well-developed monitoring capability would have minimized or prevented the Sturgeon liability we face.

- 6) With the gathering of clinical data and environmental data, we could finally get down to defining a safe dose. This is the responsibility of those observing such clinical events.

Toxicity of 2,3,7,8-TCDD in Different Species

Species, strain	Single-dose LD ₅₀ (µg/kg)	Route	Reference
Guinea pig, Hartley m,	0.6/2.0	p.o.	[3,1]
Rat, Sherman m,	22	p.o.	[3]
f,	45	p.o.	
Rat, Sprague Dawley m,	60	p.o.	[4]
f,	25	p.o.	
weanling m,	25	p.o.	
Chicken,	25-50	p.o.	[5]
Monkey, Macaca mulatta,	ca 70	p.o.	[6]
Rabbit, New Zealand albino,	115	p.o.	[3]
	275	dermal	
Mouse, C57B1/Sch strain m,	114	p.o.	[7]
Mouse, C57B1/6fh (J67) m,	284	p.o.	[1]
Dog, Beagle,	ca 200-300	p.o.	[3]
Golden Syrian hamster m,f	3000	p.o.	[8]
	1157	i.p.	
Golden Syrian hamster m	5051	p.o.	[9]

Carcinogenicity of TCDD in Rats

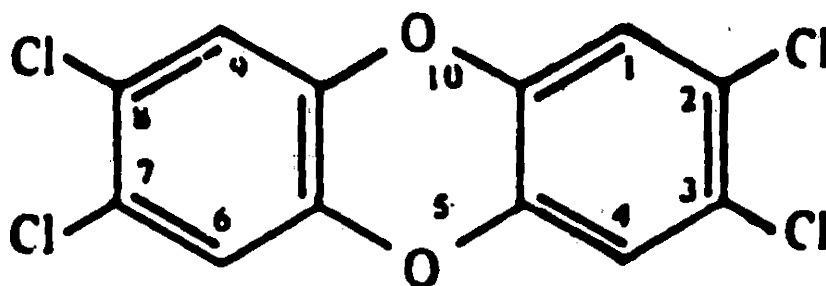
Strain	Dose µg/kg/d	Response	Ref.
Sprague Dawley m,f	0.1	Hepatocellular carcinoma, squamous carcinoma of lung, hardpalate, nasal turbinates <u>Decreased:</u> Tumors of pituitary, uterus, mamm.gland, pancreas, adrenal gland.	[55]
	0.01	Hepatocellular nodules	
Osborne Mendel m,f	0.001	No increase in tumors	[56]
	0.071	Hepatocellular carcinoma, thyroid adenoma, tissue and subcutaneous fibroma	
	0.007	Questionable increase in thyroid adenoma	
	0.0014	No increase in tumors	

Single oral LD₅₀₋₃₀ Values of Chlorinated Dioxins (µg/kg)

<u>Chlorination</u>	<u>Guinea pig</u>	<u>Mouse</u>
2,8	300 000	--
2,3,7	29 444	3 000
2,3,7,8	2	283.7
1,2,3,7,8	3.1	337.5
1,2,4,7,8	1 125	5 000
1,2,3,4,7,8	72.5	825
1,2,3,6,7,8	70-100	1 250
1,2,3,7,8,9	60-100	1 440
1,2,3,4,6,7,8	600	--
1-NO ₂ -2,3,7,8	47.5	2 000
(2,3,7,8-TCDF)*	5-10	6 000
*Data from Moore et al. [2]		

Structure and Physical Properties of TCDD

Structure



Molecular weight	322
Melting point, °C	303-305
Decomposition point, °C	980-1000
Solubility, g/L	
ortho-dichlorobenzene	1.40
chlorobenzene	0.72
Orange Herbicide	0.58
benzene	0.57
chloroform	0.37
acetone	0.11
normal-octanol	0.05
lard oil	0.04
methanol	0.01
water	2×10^{-7}

HEALTH EFFECTS FROM INDUSTRIAL ACCIDENTS INVOLVING TCDD

Year	Location	No. Affected	Organ Systems Affected:										
			Dermal	Renal	Hepatic	Neuro.	Asthenia	Blood	GI	Lipid Metab.	Immuno.	CV	Pulm.
1949	Nitro, W.Va.	228	+		+	+	+	+		+			+
1953	BASF, W. Ger.	55	+	+	+	+	+					+	+
1956	Grenoble, Fr.	17	+		+		+						
1963	Amsterdam, Neth.	44	+		-		+		+				
1968	Bolsover, Derbyshire U.K.	79	+		-		+	+	-				
1976	Seveso, Italy	134	+		+	+	+	+	+		+	-	

Code: (+) An effect was observed;

(-) An effect was not observed in patients examined (or questioned) about the effect;

() Patients were not examined or questioned, regarding any effects in the indicated organ system.

Industrial incidents associated with the manufacture of chlorinated phenols.

Year	Country	Manufacturer/Location^a	Production Product^b	Primary Source of Exposure	Number of Cases	Years from Incident to Last Observation^c	Reference
1949	United States	Monsanto/ Nitro, West Virginia	TCP	Explosion	228	4	51, 73
1949	West Germany	———/ Nordrhein, Westfalen	PCP, TCP	Occupational	17	1	11
1952	West Germany	———/———	TCP	Occupational	60	-	12
1952- 53	West Germany	Boehringer/———	TCP	Occupational	37	-	46
1953	West Germany	BSAF/ Ludwigshafen	TCP	Explosion	55	24	51, 43
1954	West Germany	Boehringer, Ingelheim/ Hamburg	TCP, 2,4,5-T	Occupational	31	9	58, 12
1956	France	Rhone Poulenc/Grenoble	TCP	Explosion	17	2	30
1956	United States	Diamond Alkalai/ Newark, New Jersey	2,4-D, 2,4,5-T	Occupational	29	13	16, 68
1956	United States	Hooker/———	TCP	Occupational (?)	-	-	46
1960	United States	Diamond Shamrock/———	TCP	Occupational (?)	-	-	46

(continued)

1962	Italy	-----/-----	TCP
1963	Netherlands	Philips-Duphar/ Amsterdam	TCP
1964	USSR	-----/-----	2,4,5-T
1964	United States	Dow Chemical/ Midland, Michigan	2,4,5-T
1965- 69	Czechoslovakia	Sokolana/-----	TCP
1966	France	Rhone Poulenc/ Grenoble	TCP
1968	United Kingdom	Coalite and Chemicals Products/ Bolsover, Derbyshire	TCP
1970	Japan	-----/-----	PCB, , 2,4,5-T
1972	USSR	-----/-----	TCP
1973	Austria	Linz Nitrogen Works/-----	2,4,5-T
1974	West Germany	Bayer/Uerdingen	2,4,5-T
1975	United States	Thompson-Hayward/ Kansas City, Kansas	TCP

Explosion	5	-	47, 51
Explosion	50	14	14, 26 51
Occupational	128	-	50, 74
Occupational	60	6	38
Occupational	78	6	54, 55 67
Explosion	21	-	46
Explosion	79	9	51, 60
Occupational	25	3	64
Occupational	1	1	81
Occupational	50	-	40, 46
Occupational	5	-	40, 46
Occupational	-	-	46

Some clinical features observed in cases of chloracne associated with production of 2,4,5-T and other chlorinated phenols.

Frequency observed	Clinical Features	Additional Notes
<u>Consistent</u>	Chloracne	In worst cases, chest and inguinal area affected and scarring generally increased.
<u>Occasional</u>	Prophyria cutanea tarda	Increased excretion of urinary uroporphyrin or coproporphyrin or both.
<u>Inconsistent</u>	Hyperpigmentation of the skin	Usually prominent on face and consisted of grayish or brownish tone to the complexion.
	Hirsutism	Noticeable between the outer edge of the eye-brow and the temple hair margin.
	Enlarged, tender liver	
	Excessive mechanical fragility of the skin	
	Neuromuscular symptoms	Severe pains in the chest and pain and weakness in extremities
	Mucous membrane irritation	Itching of the eyes and frequent tearing, hyperemia of the nasal mucosa, and inflammation of the buccal mucosa.
	Irritability	Nervousness and irritability.

The signs and symptoms observed in these accidents have included:

- skin lesions, including chloracne, hyperpigmentation and thickening of the skin
- hair loss and hirsutism
- porphyria cutanea tarda
- central and peripheral nervous disorders
- liver, kidney and gastrointestinal disturbances
- neurasthenia, including lack of drive and vigor, sleep disturbances, emotional instability and altered basic frame of mind
- respiratory and cardiac disorders
- hypothyroidism

The criteria selected as critical to the toxicologic hazard assessment of PCDDs and related compounds are the following:

- Acute lethality
- Chronic toxicity and carcinogenicity
- Teratogenicity and reproductive effects
- Mutagenic potential
- Immunotoxic effects
- Mechanisms of PCDD toxicity