Site: Syntex - Verona
ID # MOD007452154
Break: 3.3
Other: N/D

Chemical Analysis

The available methods for determining 2,3,7,8-TCDD in ug/kg (ppb) or lower concentrations are expensive, time-consuming, and difficult. The nature and use of these analyses necessitate elaborate quality control and quality assurance mechanisms (Crummett and Stehl, 1973).

In the methods used, an isotopically labeled internal standard is added to the sample before the extraction step. Studies have shown that at 12 ppb or greater the final result is independent of the percent recovery of the internal standard. Other studies have shown that the optimum recovery of 2,3,7,8-TCDD from soil is reached only after several extractions. The internal standard may be recovered more efficiently because it is added in a solvent, and, consequently, it may not be bound as tightly to the soil. This latter combination would result in variable and oftentimes erroneously low results for the native 2,3,7,8-TCDD.

Another danger in allowing recovery of an internal standard (which is added at 2.5 ppb) to be low e.g., 35%, thereby recovering only the equivalent of 0.875 ppb of labeled 2,3,7,8-TCDD) is that the signal/noise ratio for a 1 ppb native 2,3,7,8-TCDD sample would be decreased. If it is decreased to the extent that the signal representing 1 ppb of 2,3,7,8-TCDD (for 35% recovery from a 10-g sample, this would equal 3.5 ng in the final extract) is no longer within the linear range, then the percent recovery of the internal standard and the final result may not be independent. This is especially true for samples with a high background. Because of these reasons and the imprecision associated with other steps in the procedure, analytical results reflect a range rather than a specific number.

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SUPERFUND RECORDS

Recommendations for Further Study

A. Human

- Conduct additional case-control studies to determine the association between exposure to TCDD and related compounds and the incidence of soft tissue sarcomas.

- Conduct epidemiologic studies to characterize and follow populations exposed to TCDD. Determine their TCDD body burdens and the short- and long-term health effects.

- Include immunologic evaluation and evaluation of other likely target organs in epidemiologic studies of TCDD-exposed populations and develop baseline data for these end points.

- Develop better methods to analyze blood and tissue for TCDD at low concentrations. These should include radioimmunoassay (RIA) procedures and arylhydrocarbon hydroxylase (AHH) induction with biopsy material.

- Develop methods to increase excretion of TCDD after it accumulates in the body.

- Obtain better data on the toxicokinetics of TCDD in humans.

- Analyze human breast milk samples for TCDD and related compounds (to serve as an index for exposure and absorption) in exposed populations.

- Determine soil exposure/day by humans in various settings.

B. Experimental

- Conduct a series of studies related to the question of bioavailability of TCDD, to focus on differences by the type of soil, by routes of absorption, by species, by aging of soil/dioxin mixture, and by maturity of exposed animals.

- Study TCDD carcinogenicity and reproductive effects in the most sensitive animal species (guinea pig and/or subhuman primates). Carcinogenicity studies should also be conducted in non-sensitive and intermediate species to determine if the relation between the acute toxicity dose and the carcinogenicity dose is similar for all species.

- Conduct immunologic dose-response studies in young and adult animals.

- Conduct lifetime follow-up studies of immature exposed animals.

- Determine whether the ligand-receptor is integral to the mechanism(s) of action and search for antagonists and endogenous ligands in different tissues (including human cell systems in tissue culture).

- Determine whether TCDD exerts its carcinogenic potential by an initiator or promoter mechanism.

- Determine mechanisms for differences in species sensitivity.

- Study the mechanism of TCDD toxicity, particularly for cancer, as it relates to the ligand-receptor theory.

- Determine tissue TCDD levels in animals (guinea pigs) exposed in situ to TCDD-contaminated areas, thus providing further information on exposure and bioavailability.

- Prepare polychlorinated dibenzodioxin isomer standards for future laboratory work.

- Establish the role of metabolism more clearly.

- Establish the interactions of ligand-receptor complexes with macromolecules in hopes of ascertaining functional differences in these interactions between "sensitive" and "non-sensitive" species. These findings could be used in human risk assessment by providing a direct relationship between exposure and mechanism of toxicity.

C. Environmental

- Develop utilizable methods for detoxifying TCDD-contaminated soil.

- Determine ambient (background) levels of TCDD in soil, air, water, etc. (as well as in people).

- Establish "sentinel" animals as indicators of the bioavailability of TCDD in contaminated areas.

Table 1. Fetal loss in Rhesus Macaques after Oral Doses of TCDD during Weeks 4 through 6 of Pregnancy (McNulty, 1982)

Group	Total dose (ug/kg)	Schedule	Fetal losses	Gestational age of lost fetus (days)	Maternal toxicity
I	5	9 divided doses, 3 times a week	2/2	47,50	2/2
	1	Same	3/4	50,57,?	1/4
	0.2	Same	1/4	?	0/4
II	1	1 dose, day 25	3/3	48,?,?	2/3
	1	1 dose, day 30	3/3	50,51,55	3/3
	1	1 dose, day 35	2/3	53,108	1/3
	1	1 dose, day 40	2/3	100, 100	0/3
III	0	9 divided doses, 3 times a week	3/12	118,?,?	0/12

Table 2. Summary of Neoplastic Alterations observed in Sprague-Dawley Rats Fed Subacute Levels of TCDD for 78 Weeks (Van Miller et al., 1977)

Level of TCDD ng/kg	No. of animals with neoplasms*	No. of neoplasms	Diagnosis
0	0	0	--
1	0	0	--
5	5	6	1 ear duct carcinoma 1 lymphocytic leukemia 1 adenocarcinoma (kidney) 1 malignant histiocytoma (peritoneal)** 1 angiosarcoma (skin) 1 Leydig cell adenoma
50	3	3	1 fibrosarcoma (muscle) 1 squamous cell tumor (skin) 1 astrocytoma (brain)
500	4	4	1 fibrosarcoma (muscle) 1 carcinoma (skin) 1 adenocarcinoma (liver) 1 sclerosing seminoma (testes)
1000	4	5	1 cholangiocarcinoma (liver) 1 angiosarcoma (skin) 1 glioblastoma (brain) 2 malignant histocytomas (peritoneal)**
5000	7	10	4 squamous cell tumors (lung) 4 neoplastic nodules (liver) 2 cholangiocarcinomas (liver)

*10 animals per group.

**Metastases observed.

Table 3. Total and Individual Tumors in Treated Male and Female Rats of Significantly Different Incidence than Those in Nontreated Control Rats (Kociba et al., 1978)

Tumor or tumor-like lesion	Dose level (ug TCDD/kg b.w./day)							
	0		0.001		0.01		0.1	
	M	F	M	F	M	F	M	F
No. of rats examined	85	86	50	50	50	50	50	49
Hepatocellular neoplastic nodules	6	8	0	3	3	18[1]	2	23[1]
Hepatocellular carcinoma	2	1	0	0	0	2	1	11[1]
Stratified squamous cell carcinoma of hard palate or nasal turbinates	0	0	0	0	0	1	7[1]	4[1]
Keratinizing squamous cell carcinoma of lung	0	0	0	0	0	0	1	7[1]
Benign tumor of uterus	–	28	–	12	–	11	–	7[2]
Benign neoplasm of mammary gland	–	73	–	35	–	36	–	24[2]
Mammary carcinoma	–	8	–	4	–	4	0	0[2]
Pituitary adenoma	26	43	6	18	11	13	13	12[2]
Subcutaneous carcinomas	10	1	1[2]	1	5	0	6	0
Acinar adenoma of pancreas	14	0	7	1	5	0	2[2]	1
Adenoma of adrenal cortex	0	9	0	6	2	2	5[1]	5
Pheochromacytoma of adrenal gland	28	7	6	3	10	1	4[1]	2

Table 3. - continued

[1] Statistically greater than control data when analyzed by using the Fischer exact probability test, $p < 0.05$.

[2] Statistically less than control data when analyzed by using the Fischer exact probability test, $p < 0.05$.

Table 4. The Incidence of Dose Related Tumors in Osborne-Mendel Rats and B6C3F1 Mice Treated with TCDD (NTP Study, 1982a and b).

Osborne-Mendel Rats			
Tumor Type	Dose (ug/kg/wk)	Sex	Incidence
Follicular-cell adenomas, thyroid	0	M	1/69
	0.01	M	5/48
	0.05	M	6/50
	0.5	M	10/50 (P=0.001)
	0	F	3/73
	0.01	F	2/45
	0.05	F	1/49
	0.5	F	6/47
Neoplastic nodules of the liver	0	F	5/75
	0.01	F	1/49
	0.05	F	3/50
	0.5	F	12/49 (P=0.006)
Neoplastic nodules or hepatocellular carcinoma	0	F	5/75
	0.01	F	1/49
	0.05	F	3/50
	0.5	F	14/49 (P=0.001)

B6C3F1 Mice			
Tumor type	Dose (ug/kg/wk)	Sex	Incidence
Follicular-cell adenomas of the thyroid	0	F	0/69
	0.04	F	3/50
	0.2	F	1/47
	2.0	F	5/46 (P=0.009)
Hepatocellular carcinoma	0	M	8/73
	0.01	M	9/49
	0.05	M	8/49
	0.5	M	17/50 (P=0.002)
	0	F	1/73
	0.04	F	2/50
	0.2	F	2/48
	2.0	F	6/47 (P=0.014)
Lymphoma and leukemia	0	F	18/74
	0.04	F	12/50
	0.2	F	13/48
	2.0	F	20/47

TABLE 5

Daily Soil Ingestion Patterns by Age

Age Group	Soil Intested
0-9 months	0 grams
9-18 months	1 gram
1 1/2-3 1/2 years	10 grams
3 1/2-5 years	1 gram
> 5 years	100 milligrams

TABLE 6

Daily Deposition of Soil on Skin by Age

Age Group	Amount on Skin
0-9 months	0 grams
9-18 months	1 gram
1 1/2-3 1/2 years	10 grams
3 1/2-15 years	1 gram
> 15 years	100 milligrams

Table 7: Important Lesion Sites in the Kociba TCDD Study

Site:	Sex	Pathologist	Control	0.001	0.01	0.1
Stratified squamous cell carcinoma of the tongue	Males	Kociba	0/76	1/49	1/49	3/42
		Squire	0/77	1/44	1/49	3/44
Nasal turbinates/hard palate squamous cell carcinoma	Males	Kociba	0/51	0/34	0/27	4/30
		Squire	0/55	1/34	0/26	6/30
	Females	Kociba	0/54	0/30	1/27	4/24
		Squire	0/54	0/30	1/27	5/22
Hepatocellular nodules and carcinoma	Females	Kociba	9/85	3/50	18/50	34/48
		Squire	16/85	8/50	27/50	33/47
Lung keratinizing squamous cell carcinoma	Females	Kociba	0/86	0/50	0/49	7/49
		Squire	0/86	0/50	0/49	8/47

Table 8: Estimates and Approximate 95% Lower Confidence Limits for the VSD[1] of TCDD from the Kociba Study in Sprague-Dawley Rats

Lesion/Pathologist		Model[2]	Added Risk 1.E-4	Added Risk 1.E-6	Chi-squared G-O-F[4]
♂					
Male Rat Stratified squamous cell carcinoma of the tongue	Kociba	Linear*	142581 (59430)	1426 (595)	1.43
	Squire	Linear*	151793 (62642)	1518 (626)	1.60
Male rat nasal turbinates or hard palate squamous cell carcinoma	Kociba	Cubic*	8877014 (17493)	1912466 (175)	0.00
		Linear	77507 (37566)	775 (376)	0.39
	Squire	Cubic*	7757813 (11676)	1671343 (117)	2.39
		Linear	49468 (26431)	495 (264)	2.72
Female rat lung keratinizing squamous cell carcinoma	Kociba	Cubic*	8659951 (32477)	1865707 (325)	0.01
		Linear	72600 (41318)	726 (413)	0.82
	Squire	Cubic*	8126063 (26834)	1750685 (268)	0.01
		Linear	60375 (35490)	604 (355)	0.98
Female rat nasal turbinates or hard palate squamous cell carcimoma	Kociba	Linear*	49771 (25812)	498 (258)	0.49
	Squire	Linear*	37237 (20313)	372 (203)	0.20

Table 8 - Continued

Lesion/Pathologist		Model[2]	Added Risk 1.E-4	Added Risk 1.E-6	Chi-squared G-O-F[4]
Female rat liver hepatocellular carcinoma or adenoma	Kociba	Linear*	7742 (5725)	77 (57.2)	6.35
		Transf[3]	3836 (2919)	38 (29.1)	2.18
	Squire	Linear*	8649 (6074)	86 (60.7)	10.36
		Transf[3]	3760 (2763)	38 (27.6)	4.30

[1] Entries are virtually safe dose (VSD) Linear-cubic lower confidence bounds (LCB) in fg/kg b.w./day by using the multistage model.

[2] Linear Model: P(d)=1-e(-a-b*d) Cubic Model: P(d)=1-e(-a-c*d**3).

[3] A multistage model is fitted to the average liver concentration of TCDD, and safe doses are transformed by using the relationship:

Administered dose = Liver dose/510.297

The divisor is the least-squares slope between the administered and the average liver dose of TCDD for control and the two lowest doses.

[4] G-O-F = goodness of fit.

*best fit.

Table 9: Estimates and Approximate 95% Lower Confidence Limits for the VSD[1] of TCDD from the NCI/NTP Study

Lesions:	Model[2]	Added Risk 1.E-4	Added Risk 1.E-6	Chi-squared G-O-F [3]
Male rat thyroid				
Follicular-cell adenoma	Linear*	40291 (21435)	403 (214)	4.81
Female rat thyroid				
Follicular-cell adenoma	Cubic*	7142868 (36711)	1542868 (367)	0.48
	Linear	75737 (34895)	757 (349)	0.79
Female rat liver				
Neoplastic nodules	Linear*	1442863 (19298)	105571 (193)	1.31
	Linear	31520 (18764)	315 (188)	1.61
Nodules and Carcinomas	Quadratic*	1338200 (16523)	133820 (165)	1.31
	Linear	25552 (16001)	256 (160)	1.74
Male Mouse Liver				
Hepatocellular Carc.	Linear*	26293 (15147)	263 (151)	1.01
Adenomas and Carc.	Linear*	13394 (8633)	134 (86)	0.14
Female Mouse Liver				
Hepatocellular Carc.	Linear*	246021 (121594)	2460 (1216)	0.74
Adenomas and Carc.	Linear*	145013 (77876)	1450 (779)	2.59
Female Mouse Thyroid				
Follicular-Cell Adenoma	Linear*	301051 (139090)	3011 (1391)	3.75

Table 9 - Continued

Lesions:	Model[2]	Added Risk 1.E-4	Added Risk 1.E-6	Chi-squared G-O-F [3]
Female Mouse Sarcoma				
Subcutaneous Tissue	Lin-Cubic*	430263 (142803)	4303 (1428)	0.05
	Linear	295289 (142777)	2953 (1427)	0.06
Female Mouse Lymphoma and Leukemia	Linear*	102852 (54271)	1028 (543)	0.02

[1] Entries are virtually safe dose (VSD) lower confidence bounds (LCB) in fg/kg b.w./day by using the multistage model.

[2] Linear: P(d)=1-3(-a-b*d) Quad: P(d)=1-3(-a-c*d**2)

Cubic: P(d)=1-3(-a-f*d**3) Lin-Quadratic: P(d)=1-3(-a-b*d-c*d**2)

Lin-Cubic: P(d)=1-3(-a-b*d-f*d**3)

[3] G-O-F = goodness of fit.

* best fit.

Table 10: Concentrations of TCDD in Soil That Are Projected to Produce the Maximum Allowable Residues in Foods

Food	TCDD in fat, pg/g	Observed Ratio[1]	Soil, pg/g
Beef[2]	7.9	0.39	20
Beef(cull dairy)[3]	7.9	0.10	79
Pork	22.7	1.86	12
Milk	2.5	0.40	6.2

[1] Concentration of polybrominated biphenyls (PBB) in product/concentration of PBB in soil (Fries and Jacobs, 1983).

[2] Includes dairy cattle that have never lactated.

[3] Older cows. Younger cows would approach the values for beef cattle.

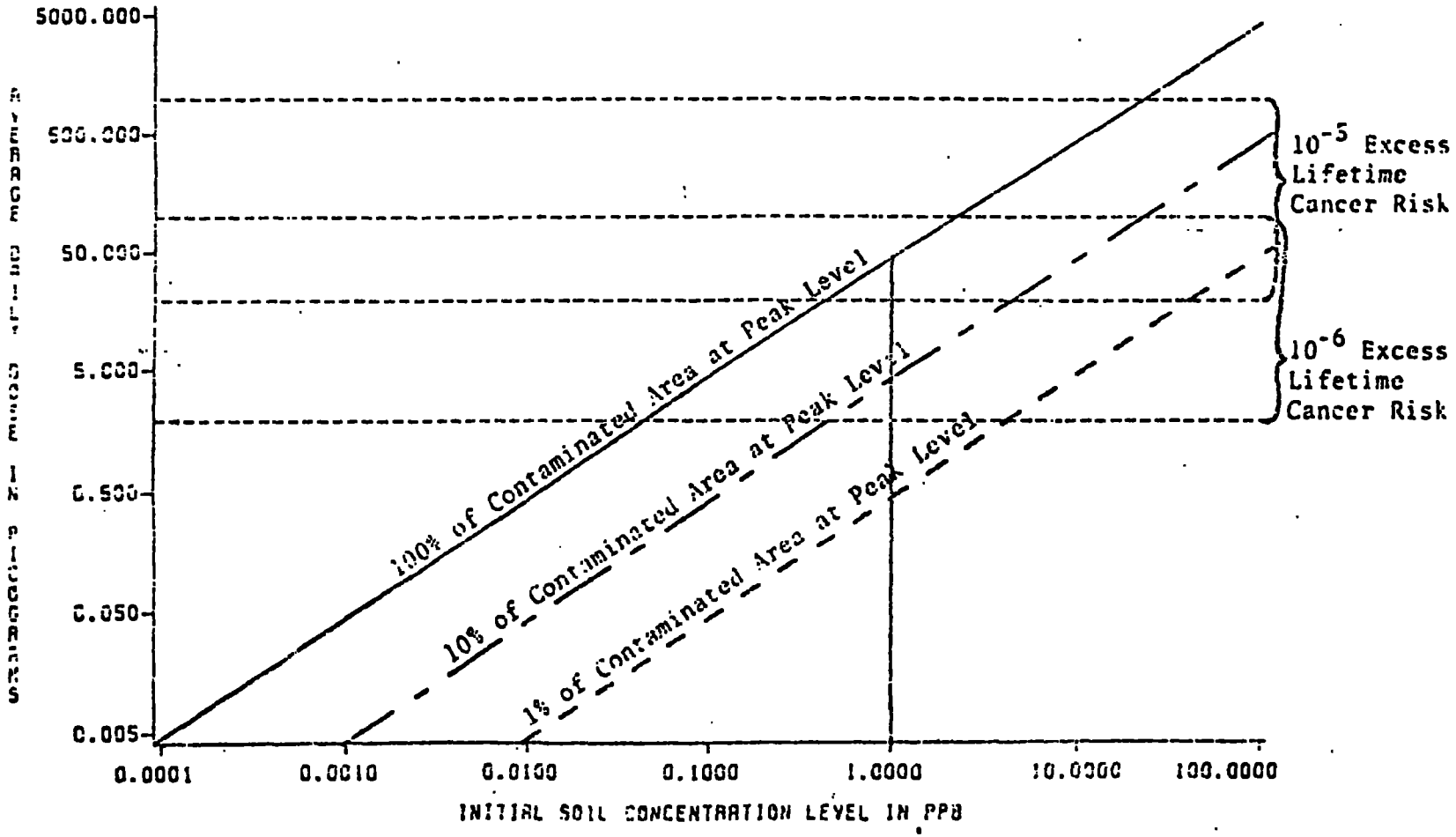
Table 11: Daily Consumption, Fat Content and Allowable Concentration of TCDD in Fat to Maintain Human TCDD Intake Below 100 pg/day/person

	Consumption, g/day	Fat,%	Fat consumption, g/day	Allowable TCDD in fat, pg/g[1]
Beef	105	8-12	8.4-12.6	7.9
Pork	54	6-8	3.2-4.3	22.7
Milk	1000	4	40	2.5

[1] Based on the higher fat intake value.

FIGURE 1

ESTIMATED AVERAGE DAILY DOSE CORRESPONDING TO INITIAL TCDD – SOIL CONTAMINATION LEVELS



EXCESS LIFETIME RISK OF DEVELOPING CANCER CORRESPONDING TO INITIAL TCDD – SOIL CONTAMINATION LEVELs

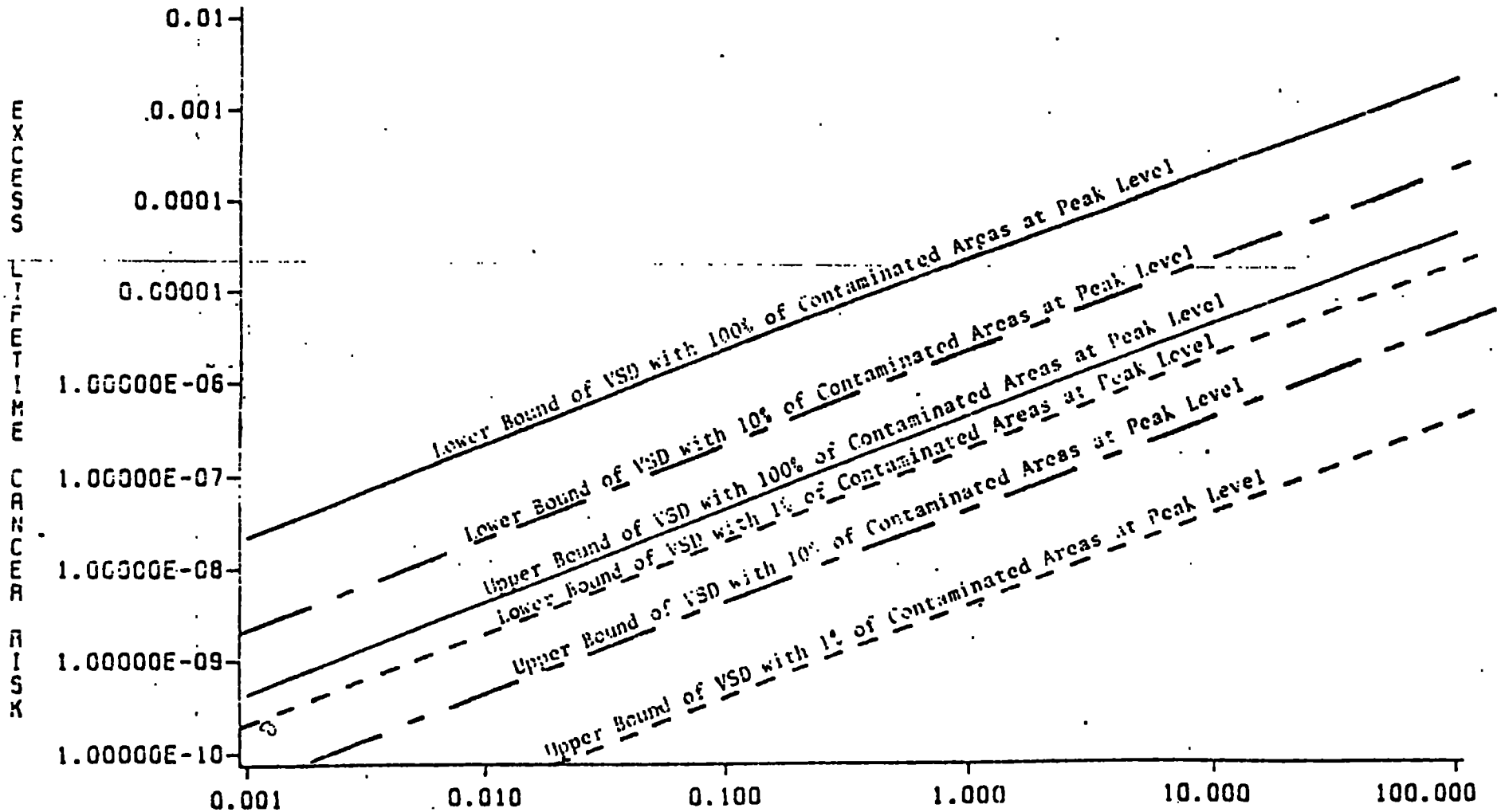
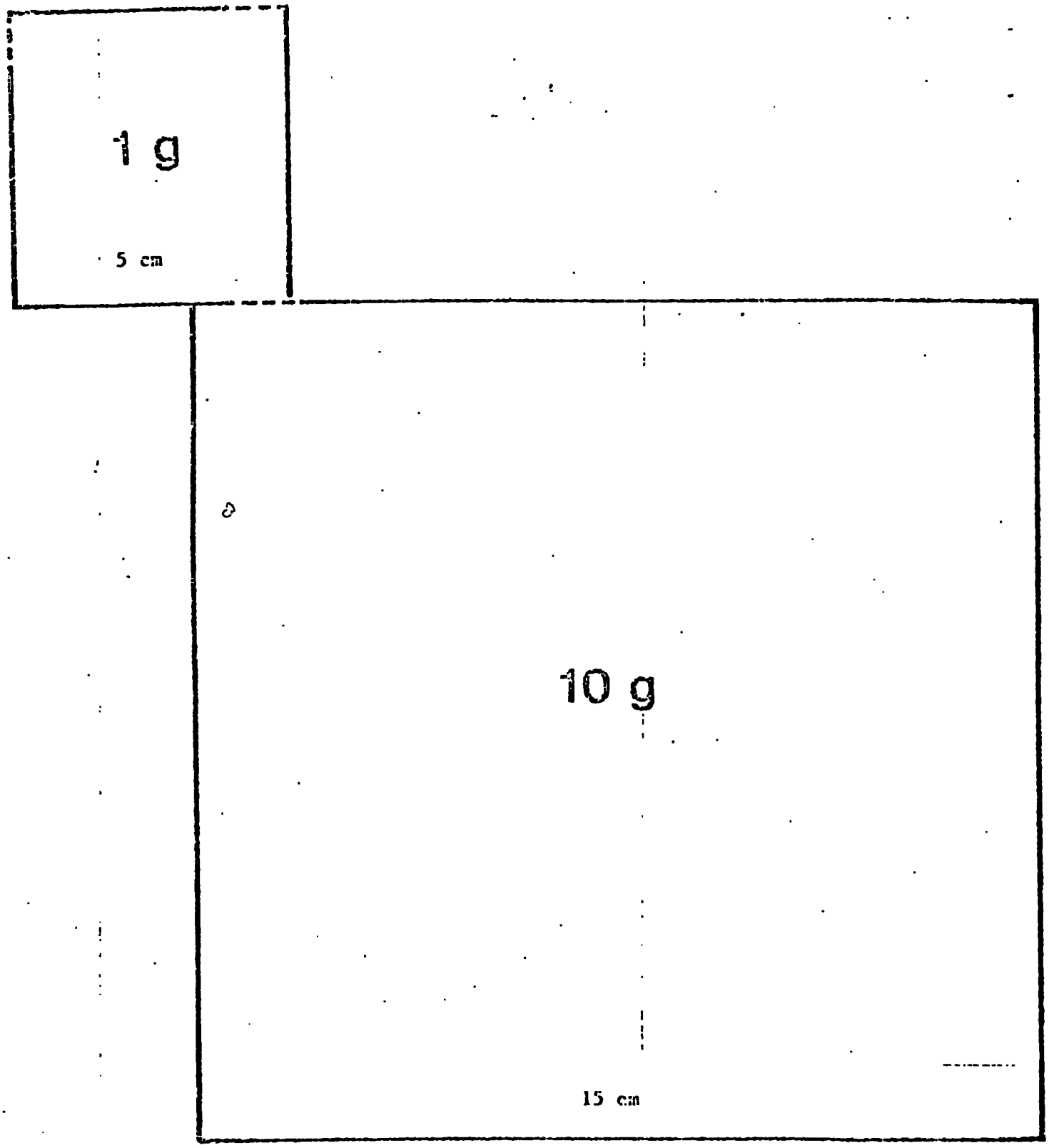


FIGURE 2

FIGURE 3



Legends for Figures

Figure 1 This figure illustrates the average daily dose of TCDD which would be received if 100, 10, or 1% of the accessible soil were contaminated with the peak recorded level of TCDD. The boundaries for an excess lifetime cancer risk for 10^{-5} and 10^{-6} are also illustrated.

Figure 2 This figure illustrates the lower and upper bounds of the virtually safe dose for a lifetime excess cancer risk. This information was derived from the calculations developed from animal data (Table 8 and 9). At the concentration of 1 ppb if 100% of the accessible soil contained TCDD at this concentration the area of risk which is bordered by the upper and lower bound of the virtually safe dose does not represent an unacceptable cancer risk given the fact that the background cancer incidence in the general population is of a much higher order of magnitude. If less that 100% of the soil was contaminated this risk would even be further reduced. However, at levels much above 1 ppb the risk would become unacceptable.

Figure 3 Surface area covered by 1 and 10 g of dirt less than 1 mm thick.

Figure 4 Average surface area of the palm of one hand of 2- and 4-year old children, adult females and males.

Appendix I

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Appendix II

Date: August 1, 1983

From: Mathematical Statistician, BRAP

Subject: Teratogenic and Reproductive Effects of 2,3,7,8-TCDD as Noted by Murray et al.

To: Director, BRAP

I have previously reviewed the article by Murray et al. entitled "Three generation reproduction study of rats given 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the diet." I must report that the analysis of the results from this study are suspect. Several reasons lead me to this conclusion. First, in a reanalysis of these data using trend tests instead of paired comparisons, the results were different (Nisbet and Paxton, Am. Stat., 36[3]. Most notably, Nisbet and Paxton concluded that the 0.001 dose level (not the 0.01 dose level as is stated in the synopsis from Kimbrough) is not a NOAEL, whereas Murray et al. concluded 0.001 was a NOAEL. In addition, in the table below, you will note that the fertility index increases with each subsequent generation in the control and low dose groups, but remains constant in the 0.01 dose group. Murray et al. and Nisbet and Paxton both conclude there is decreased fertility in the 0.01 dose group as compared to the control group. Without more information concerning what is a normal fertility index in these animals and just based upon these data, I cannot agree with their result. Including these remarks and noting the difficulty of the design for analysis, I would conclude there is insufficient evidence for an effect at the 0.01 dose.

C.J. Portier

TABLE 1

Fertility Index (FI[1] of Rats Given TCDD

	Micrograms TCDD/kg/day							
	0		0.001		0.01		0.1	
Generation	FI	%	FI	%	FI	%	FI	%
f0								
first mating	14/32	44	10/20	50	12/20	60	3/31	10
second mating	21/32	66	14/19	74	15/20	75	1/30	3
f1	22/26	85	15/17	88	12/21	57		
f2	28/32	88	20/20	100	11/20	55		

[1] The fertility index used in this table is the number of females delivering a litter divided by the number of females placed with a male.

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