Monsanto

FROM (NAME & LOCATION): Medical, A2SA

DATE: September 28, 1972

SUBJECT:

REFERENCE:

TO: D. R. Miller
T3F

cc: W. R. Richard - T3A
E. S. Tucker - T2S
R. E. Keller - T1B
J. S. Metcalf - E1SF
W. B. Papageorge - B2NK
R. E. Kelly/J. T. Garrett/
E. P. Wheeler - A2SA

Attached are copies of acute toxicity tests conducted with rainbow trout.

From the test results, approximate 96-hour TLm values have been calculated using tables prepared by Weil /Biometrics 8: 249-263 (1952)/. These values are shown in the accompanying table which also summarizes the fish studies.

The response to fraction D (3 ring, ex isomerized) was somewhat erratic and Dr. Goode at Industrial Bio-Test has reasons to question the validity of the data. Consequently, he plans to repeat the test with fraction D at Bio-Test's expense and will let us know the results at a later date.

On the basis of the data, fraction E is least toxic, fractions B and C are somewhat more toxic, and fractions A, D and F are essentially equal in toxicity and the most toxic.

GJL

George J. Levinskas

/bks

att.

IN-10 REV. 11-68

Sample	Mortality* at a ppm concentration of 0.01	0.1	1.0	10	100	96-Hour TLm in ppm**
Hi-boiling (A)	0	2	4	10	10	0.79 (0.30-2.10)
Cut #4 (B)	0	0	1	10	10	2.51 (.158-3.98)
Phenyl ether (C)	1	0	0	10	10	3.16***
3-Ring, ex iso (D)	3	1	3	4	6	1.00****
3-Ring, ex uniso (E)	0	0	0	2	10	19.9 (10.8-36.8)
Treated Aroclor 1260 (F)	2	0	5	10	10	1.0 (0.38-2.61)

* Groups of 10 fish exposed
** 95% confidence limits are shown in parentheses.
*** One death at 0.01 ppm ignored in calculations.
**** Estimated, response too erratic for calculation.

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

RESULTS OF FOUR-DAY STATIC FISH TOXICITY STUDIES
RAINBOW TROUT
IBT. NO. A-1973 BTL. NO. 72-64

Test Material: Treated AROCLOR 1260 PFP OR179451F
Description: Cloudy White Viscous Liquid
Form Administered: 1.0 and 10.0% (w/v) solution in acetone

Concentration of Test Material (ppm)	Parameter	Rainbow Trout Elapsed Time (hours) 1-6	24	48	72	96	Total
100.0	pH	-	6.6	6.9	-	-	-
	DO	-	8.3	7.7	-	-	-
	°C	-	13.0	12.8	-	-	-
	Survivors	10	8	0	0	0	0
10.0	pH	-	6.5	6.8	-	-	-
	DO	-	4.9	6.0	-	-	-
	°C	-	13.0	12.8	-	-	-
	Survivors	10	1	0	0	0	0
1.0	pH	-	-	6.4	-	-	-
	DO	-	-	2.7	-	-	-
	°C	-	-	12.8	-	-	-
	Survivors	10	10	5	5	5	5
0.1	pH	-	-	-	-	-	-
	DO	-	-	-	-	-	-
	°C	-	-	-	-	-	-
	Survivors	10	10	10	10	10	10
0.01	pH	-	-	7.1	-	-	-
	DO	-	-	3.9	-	-	-
	°C	-	-	12.8	-	-	-
	Survivors	10	10	8	8	8	8

Four-Day TL_{50} $\cong$ 1.0 ppm

MONS 031645

Comments: 100 ppm - Cloudy Water

Monsanto INDUSTRIAL CHEMICALS COMPANY

FROM (NAME & LOCATION): J. F. Pysz - Q3C

DATE: October 15, 1975

SUBJECT: TOXICITY OF POLYCHLORINATED DIBENZOFURANS

REFERENCE:

CC: M. A. Terpstra - Q3C
M. R. Bagley - Q3C
D. J. Kalota - Q3C
J. P. Mieure - T2F

TO: C. C. Sisler
R2E

A literature search was made on the toxicity of polychlorinated dibenzofurans (PCDF). The literature, although sparse, does indicate that polychlorodibenzofurans are toxic. They are more toxic than are polychlorinated biphenyls but are approximately ten times less toxic than tetrachlorodibenzo-p-dioxin (TCDD). Data on the lethality of TCDD[14] reveal that a single oral LD_{50} ranges from 0.0006 mg/kg in male guinea pigs to 0.115 mg/kg in rabbits of mixed sex. Based on the available literature, the order of PCDF toxicity has been estimated to be:

Dichloro=Tetrachloro>Trichloro>Octachlorodibenzofuran.

The toxic effects reported include: (1) skin irritation (chloroacne) to humans[11] and rabbits[8,9]; (2) lesions resembling those produced by chick edema[9]; (3) edema formation in rabbits[8]; (4) liver damage in rabbits[5,8]; (5) death in chick embryos[2,3]; and (6) death to salmon[1].

A number of references indicate that PCDF are more toxic than polychlorobiphenyls (PCB) and are responsible for some of the toxic effects attributed to PCB[3,4,6,7]. Vos[2] conducted a chick embryo assay and found that a chromatographic fraction from two polychlorinated biphenyl preparations (Phenoclor DP6 and Clophen A6) containing tetrachloro, pentachloro, hexachloro and heptachlorodibenzofuran were highly toxic. A corresponding fraction from Aroclor 1260 which did not contain those compounds did not have a significant toxic effect on the chick embryo. Bowes[3] also attributed laboratory embryonic deaths to the chlorinated dibenzofurans in PCB.

Zitko[1] reported a median mortality rate of 120 days for juvenile Atlantic salmon which were fed dry fish food containing:

Dichlorodibenzofuran - 2.7 µgm/gm
Trichlorodibenzofuran - 5.7 µgm/gm
Tetrachlorodibenzofuran-2.8 µgm/gm
Octachlorodibenzofuran-9.1 µgm/gm

These data indicate the order of toxicity to be:

Dichloro=Tetrachloro>Trichloro>Octachlorodibenzofuran.

In contrast, a single dose of 2,8-dichlorodibenzofuran (122 mg/kg) administered to brook trout caused no fatalities[12].

Liver necrosis resulted following a single oral dose (0.5-1.0 mg/kg) of tri and tetrachlorodibenzofuran in rabbits. In comparison, a dose of

0.05-0.1 mg/kg of 2,3,7,8-tetrachlorodibenzo-p-dioxin produced liver necrosis and chloracne[5]. These data indicate that PCDD is perhaps 10 times more toxic than PCDF. The PCDF's were also found to be acne-inducing agents[8,10].

It is believed that toxicological studies on PCDF's are now in progress or will be in the near future by the Federal Drug Administration. There is also an indication that some toxicity studies on PCDF's have already been made. The source of the study, however, has not been clearly defined.

The sources used for this literature search were chemical abstracts and a bibliography in Environmental Health Perspectives, 1973, (5), pp 283-312.

John F. Pysz

db
Attach.

POLYCHLORINATED DIBENZOFURANS

REFERENCES

Toxicity

1. Chlorinated dibenzylfurans are more toxic than polychlorinated biphenyls. A median mortality rate of 120 days was observed in juvenile Atlantic salmon fed on dry fish food containing

   Dichlorodibenzofuran - 2.7 ugm/gm
   Trichlorodibenzofuran - 5.7 ugm/gm
   Tetrachlorodibenzofuran - 2.8 ugm/gm
   Octachlorodibenzofuran - 9.1 ugm/gm

   [Order of toxicity: Di≥Tetra>Tri>Octa]

   Zitko, V., Choi, D.M.K., Bull. Environ. Contam. Toxicol., 73, 10(2), 120-2.

2. A chick embryo assay indicated a high toxicity chromatographic fraction of 2 polychlorinated biphenyl preparations - Phenoclor DP6 and Clophen A6, containing tetrachlorodibenzofuran, pentachlorodibenzofuran, hexachlorodibenzofuran, and heptachlorodibenzofuran. A corresponding fraction from Aroclor 1260 did not contain these compounds and did not have a significant toxic effect on the chick embryo.

   Vos, J.G., Koeman, J.H., VanderMaas, TenNoever deBraun, M.D., DeVos, R.H., Food Cosmet. Toxicol., 1970, 8 (6), 625-33 (Eng.).

3. Embryonic deaths have been recorded in the laboratory among birds treated with PCB. These deaths have been attributed to chlorinated dibenzofuran contaminants. Also, birth defects in wild populations of birds and sea lions are believed caused by chlorinated dibenzodioxins.

   Bowes, G.W., Simoneit, B.R., Burlingame, A.L., DeLappe, B.W., Peakall, P.B., Risebrough, R.W., Environ. Health Perspect. (#5), 191 (1973).

4. Dibenzofurans were implicated as being responsible for some of the toxic effects attributed to PCBs. Waldbott, G.L., "Effects of Environmental Pollutants", C. V. Mosby Co., St. Louis, Mo., 1973.

5. The tri and tetrachlorodibenzofuran single oral liver necrotic dose (0.5 to 1.0 mg/kg) in rabbits.

   The 2,3,7,8-tetrachlorodibenzo-p-dioxin caused lethal liver necrosis and chloracne in rabbits at a dose range of 0.05 to 0.1 mg/kg.

   Fishbein, L., "Polychlorinated Biphenyls and the Environment,", Report No. ITF-PCB-72-1 (com-72-10419), Interdepartmental Task Force on PCBs, Washington, D.C., May 1972, pp 122-151.

6. Some commercial PCB mixtures may contain trace amounts of dibenzofurans or other toxic impurities. These may be the cause of some toxic effects of the PCBs.

Hammond, A.L., Science, 175, 155-156 (January 14, 1972).

7. The most toxic impurities in polychlorinated biphenyls were found to be chlorinated benzofurans.

Vos, J.G., Tijdschr. Diergeneesh, 97, (22), 1378-85 (1972)(Neth.).

8. The major acnegenic action of crude PCB mixtures originates from chlorinated dibenzofurans. The probable contribution of chlorinated dibenzofurans and pure PCB to the toxicity of technical PCB preparations in rabbits.

	Furan	PCB
Chloracne	++	+
Edema Formation	++	-
Liver Damage	++	+
Hepatic Porphyria	-	++

Vos, J.G., Notenboom-Ram, E., Toxicol. Appl. Pharmacol 23, 563-578 (1972).

9. Lesions resembling those produced by chick edema factor were traced to a PCB contaminant, chlorinated dibenzofurans.

Anonymous, Food Cosmet. Toxicol. 9 (4), 568-571 (1971).

10. Trichlorodibenzofuran, tetrachlorodibenzofuran and 2,3,6,7-tetrachlorodibenzodioxin were especially effective acne-inducing agents on rabbit ears. The tetrachlorodibenzodioxin was the most toxic - concentrations of 0.01 to 0.002%. Higher concentrations caused liver necrosis and death. Single oral administration of 0.05 to 0.1 mg/kg body weight caused death in 1-2 weeks.

Kimmig, J., Schulz, K.H., Naturwiss, 44, 337-8 (1957)(Ger.).

11. Trichloro and tetrachlorodibenzofurans, and tetrachlorodibenzo-p-dioxin were found to be active skin irritants to humans.

Kimmig, J., Schulz, K.H., Dermotologia, 115 (4), 540-6 (1957) (Ger.).

12. A single dose of 2,8-dichlorodibenzofuran 122 mg/kg administered to brook trout caused no mortality. Low acute toxicity and residual levels are due to poor adsorption in the gut.

Zitko, V., Wildish, D.J., Hutzinger, O., Choi Puk, Environ. Health Perspect., 1973, (5), 187-9 (Eng.).

13. Pentadichlorodibenzofuran and 2,3,7,8-tetrachlorodibenzodioxin were given orally to female mice and their hepatic enzyme-inducing activities were evaluated. Both were highly active in reducing the hexobarbitol sleeping time in mice.

The furan was 170 times and dioxin was 1250 times as effective as PCB based on their RD_{60} values (values which reduce sleeping time to 60% levels of the control)

Araki, Yasunoi, Fukuoka-Igaku-Zasshi, 1974, 65 (1), 61-4.

14. Toxicology of chlorinated dibenzo-p-dioxins.

Schwetz, B.A., Norris, J.M., Sparschu, G.L., Rowe, V.K., Gehring, P.J.,'Chlorodioxins - Origin and Fate', Advances in Chemistry, Series No. 120, American Chemical Society, pp 55-69 (1973).