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FROM (NAME LOCATION PHONE) Dept. of Medicine & Environmental Health - P.L. Wright, G2WF

DATE February 3, 1981 cc G.J. Levinskas, G2WF

SUBJECT Tumorigenicity of Hexachlorodibenzo-p-dioxin (HCDD)

REFERENCE

TO G. Roush, Jr., M.D., G2WG

The National Cancer Institute has issued two reports[1,2] on the tumorigenicity of HCDD following oral (gavage) or dermal administration. A mixture of 1,2,3,6,7,8 HCDD and 1,2,3,7,8,9 HCDD when administered to male and female rats and male mice at doses up to 5 µg/kg/week and to female mice at doses up to 10 µg/kg/week resulted in statistically significant increases in hepatocellular adenomas in male and female mice and hepatic neoplastic nodules in female rats. Male rats were not affected. The incidence of hepatocellular carcinoma was variable but was not statistically significantly increased in any group. The incidence of other neoplastic lesions did not differ among control and treated animals.

In a previous study, Kociba[3] reported an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung in rats fed diets providing 0.1 µg 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) per day. Rats given 0.01 µg/kg/day had increased liver (hepatocellular nodules) and lung (focal alveolar hyperplasia) lesions.

The HCDD used in the NCI study contained approximately 0.1 ppm TCDD and 0.4 to 1.4 ppm pentachlorodibenzo-p-dioxin (PCDD). These are assumed to have been predominantly 2,3,7,8 containing isomers. Thus, it is possible that the animals in the NCI study could have been exposed to 0.005 µg TCDD/week and 0.02 to 0.07 µg PCDD/week. These levels approach the tumorigenic levels of TCDD in the Dow study. The relative tumorigenicity of PCDD has not been reported making it impossible to directly evaluate the effects of the TCDD and PCDD contamination in the HCDD used in the NCI study.

A 90-day rat feeding study[4] with pentachlorophenol containing 19 ppm HCDD has been reported. In that study, increased liver weights were observed at pentachlorophenol dosages as low as

1 Technical Report Series No. 198, NTP No. 80-12 (1980).

2 Technical Report Series No. 202, NTP No. 80-13 (1980).

3 Kociba, et al (Dow) TAP 46:279-303 (1978).

4 Johnson, et al (Dow) Envir. Health Perspec., Sept., 1973, pp. 171-175.

3 mg/kg/day and microscopic liver lesions were seen at 30 mg/kg/day. With chemically pure pentachlorophenol, liver weight increases were observed at 10 mg/kg/day, but no microscopic lesions were found even at 30 mg/kg/day. The commercial pentachloro sample tested[4] would have contributed a calculated 0.057 µg HCDD/kg/day or approximately 0.4 µg/kg/week in a pentachlorophenol dosage that induced evidence of toxicity after 90 days. This dosage is well below the lowest level (1.25 µg/kg/week) of HCDD that increased the incidence of neoplastic nodules in female rats; male rats were not affected at dosages as high as 5 µg HCDD/kg/week.

An important difference exists between the HCDD isomer composition of the NCI test material and the HCDD composition anticipated from our pentachlorophenol production conditions. The isomers present in the NCI test material were both chlorinated in the 2,3,7,8 positions. Chlorination in these positions produces the most toxic dioxin isomers. An industry composite pentachlorophenol sample, believed to be representative of Monsanto pentachlorophenol, has been analyzed and found to contain less than 10 ppm HCDD. The HCDD isomer composition in pentachlorophenol (see attached, J. Wilson to P. Wright, 1/20/80) would be expected, on a statistical basis, to contain only 12.5% of an isomer chlorinated in the 2,3,7,8 positions.

It is unlikely that any significant risk of liver tumor induction due to HCDD contamination in pentachlorophenol exists. To approach an exposure to HCDD from pentachlorophenol equivalent to that producing tumors in the NCI study, would result in early indications of other toxic manifestations resulting from pentachlorophenol exposure.

Paul L. Wright

alw

attachment

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JAN 2 1 1980

FROM (NAME—LOCATION—PHONE) J. D. Wilson - N3A - 4-5274

DATE : January 20, 1980

SUBJECT : Hexachlorodibenzodioxins in Pentachlorophenol

REFERENCE :

TO : P. L. Wright - G2WF

cc: P. J. Arnall - B3NJ
C. F. Callis - B3CA
H. W. Kilbourne - N3A
D. P. Roman - N3B

Attached is a copy of an analysis of an industry-composite pentachlorophenol sample. It is believed to be representative of Monsanto's pentachlorophenol, at least that produced after about 1960.

Regarding your question on hexachlorodibenzodioxin isomer analyses: as far as I know, no such work has been done. I am not sure that anyone in the world has demonstrated the capability to do this. As far as I know, only the two-isomer mixture tested by NCI has been isolated and identified.

If the hexachlorodibenzodioxins in "penta" are formed by condensation of the predominant tetrachlorophenol (2,3,4,6-TeCP), and if they are formed in statistical amounts, we would expect to find six (of the twelve possible) isomers, in this distribution:

1,2,3,6,7,9 - 25%	1,2,3,6,8,9 - 12.5%
1,2,3,6,8,9 - 25%	1,2,4,6,7,9 - 12.5%
1,2,3,6,7,8 - 12.5%	1,2,4,6,8,9 - 12.5%

The NCI mixture was formed by condensation of the tetrachlorophenol isomer (2,3,4,5 - TeCP) not normally present in penta.

Jim

J. D. Wilson

/dh

IN - 10 (REV. 8/77)

O. Hicks - T2F

February 3, 1978

cc: R. G. Kaley,
P. R. Michael
J. P. Mieure

Pentachlorophenol - Producers Composite

TO : D. P. Roman - N2B

John Moore NIEHS

Analysis of the most recent producers composite of Penta (MB-456) has been completed. The data are comparable to previous composites and are listed below.

Octachlorodibenzo-p-dioxin	1410 ppm
Heptachlorodibenzo-p-dioxin	505
Hexachlorodibenzo-p-dioxin	9.4
Pentachlorodibenzo-p-dioxin	0.03
Tetrachlorodibenzo-p-dioxin	n.d. <0.01
Trichlorodibenzo-p-dioxin	n.d. <0.01
Octachlorodibenzofuran	182
Heptachlorodibenzofuran	116
Hexachlorodibenzofuran	6.8
Pentachlorodibenzofuran	1.1
Tetrachlorodibenzofuran	0.7
Trichlorodibenzofuran	0.02
Pentachlorobenzene	125
Hexachlorobenzene	30
PCB's (total)	n.d. <1

O. Hicks

/sf

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DEPARTMENT OF MEDICINE & ENVIRONMENTAL HEALTH

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February 6, 1981

TO: BIOHAZARDS COMMITTEE

Drs. L. Golberg
M. Kuschner
R. Olson

Enclosed is some additional information relative to the dioxin and furan content in pentachlorophenol. During our last meeting we reviewed the NCI reports of the tumorigenicity of hexachlorodibenzo-p-dioxin. I have included the summaries from these studies.

At the February 19 meeting, we would like your recommendations on the following issues:

1) What possible health risks may have resulted from occupational exposure to pentachlorophenol. What future follow up programs should be undertaken to responsibly monitor future developments among this population.

2) What is your assessment of Monsanto's future liability for cancer development among this population.

3) Are additional studies warranted, e.g., the characterization of the HCDD isomer distribution pentachlorophenol?

We shall look forward to your discussion of this matter.

Sincerely,

Paul L. Wright, PhD

PLW:alw

cc: Dr. G. Roush, Jr.
Dr. G.J. Levinskas

enclosure