

Monsanto

FROM NAME LOCATION PHONE

Dept. of Medicine & Environmental Health R.C. Dirks, G2WD, 4-8818

DATE: December 27, 1982
SUBJECT: Toxicology "time lines"
REFERENCE: Xylene, 2,4,5-trichloro-
 phenoxyacetic acid
TO: G.J. Levinskas

cc T.W. Fuhremann
F.R. Johannsen

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Attached are the toxicology "time lines" for the two referenced materials. The dates and references are, according to my literature review, the first substantive studies to indicate that the mentioned effects may be caused by each material. The dates should not be considered to be the point at which the effects were proven to be a result of exposure. Many of the effects cited (i.e. the teratogenicity of 2,4,5,-T) have not yet been generally accepted as fact.

Negative findings have not been generally included in the time lines. Thus, if certain organs, tissues or organ systems have not been mentioned, it is either because they were not examined or, more probably, because they were not affected in the particular studies discussed.

Apart from the above explanations, the information included in the time lines should be fairly self-explanatory. Please let me know if these are acceptable.

Richard C. Dirks

/cld
enc.

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2,4,5-trichlorophenoxyacetic acid

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) is a herbicide which was manufactured by Monsanto from 1946 until 1970. Until the late 1960s and early 1970s there was very little toxicologic information available.

Effects attributed to acute exposure to 2,4,5-T include eye and respiratory tract irritation, headaches, dizziness and nausea, muscle discomfort and, most frequently, chloracne. Chronic effects in humans attributed to 2,4,5-T include all of the previously mentioned signs and liver disorders, jaundice, edema of the face and hands, loss of appetite, weight loss, bleeding of the gums and hematologic (blood) effects. Chronic studies in rodents have reported thymic and splenic atrophy, hypocellularity of bone marrow and lymph nodes, renal effects and negative behavioral (learning) ability.

Several reports of positive mutagenic activity are published, but the weight of evidence shows 2,4,5-T to be both non-mutagenic and non-carcinogenic. Many of these studies (and others) are compromised by significant levels of TCDD in the 2,4,5-T sample.

The most oft-cited effect of 2,4,5-T besides chloracne is teratogenicity. The effects appear to be very species-specific and again are confounded by TCDD contamination. This issue remains controversial.

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2,4,5-Trichlorophenoxyacetic Acid

<u>Date</u>	<u>Effects Observed/Comments</u>	<u>Reference</u>
1899	Chloracne described, believed to be caused by free chlorine.	Herxheimer, K.: Munch Med. Wschr. 46:278, 1899
1918	Chloracne attributed to certain chlorinated hydrocarbons.	Wauer, H.: Zbl. Gew. Hyg. 6:100, 1918
1936	One of the first reports of chloracne in chlorinated biphenyl plant worker. Also reported lassitude, loss of appetite, loss of libido.	Jones, J.W. and Alden, H.W.: Arch. Derm. Syph. 33:1022-1034, 1936
1936	Liver effects ("acute yellow atrophy") from certain chlorinated naphthalenes.	Flinn, F.B. and Jarvik, N.E.: Proc. Soc. Exp. Biol. Med. 35:118-120, 1936
1946	Initiation of 2,4,5-T process at Krummerich Plant, Sauget, Ill.	Monsanto World Hdqts. News 24(3), 1980
1948	First registration of 2,4,5-T on March 2 by Am. Chem. Prod. Co., Ambler, PA.	"Report on 2,4,5-T" Panel on Herbicides, Presidents Science Advisory Comm., 1970
1948	Initiation of 2,4,5-T production at Monsanto's Nitro, West Virginia plant.	Monsanto World Hdqts. News 24(3), 1980
1949	Accident at Nitro plant. Approximately 121 people involved. Complaints included:	Monsanto World Hdqts. News 24(3), 1980

1. chloracne
2. eye & respiratory tract irritation
3. headache
4. dizziness & nausea
5. muscle discomfort
6. liver disorders

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All except chloracne gradually disappeared.

1949	Report of "150 to 280" workers in four different factories with chloacne. Also:	Teleky, L.: Klin. Wschr. 27:249-257, 1949
	1. loss of appetite 2. nausea 3. edema of face & hands 4. abdominal pain & vomiting 5. jaundice 6. at autopsy → acute yellow atrophy	

Many other reports from 1936-49 cited.

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Date	Effects Observed/Comments	Reference
1950	Dow Chemical Company initiates acute testing program with 2,4,5-T, but <u>does not</u> release the information <u>until</u> some of it is published piecemeal in '54.	Panel on Herbicides, 1970
1953	Published toxicology information: 1. inferred LD50 (dog) = 100 mg/kg 2. 20 mg/kg/day killed 4 dogs in 11-75 days 3. 10 mg/kg/day - no deaths in 90 days (dogs) a. weight loss b. leg stiffness c. weakness d. gum bleeding/slight hematologic effects (↓ lymphocytes) e. liver - focal necrosis (not thought to be treatment related)	Drill, V.A. and Hiratzka, T.: AMA Arch. Indus. Hyg. Occ. Med. 7:61, 1953
1954	Some Dow acute toxicity (LD50) information published: rats - 500 mg/kg, mice - 389, guinea pigs - 381, chicks - 310. 1000 mg/kg fatal to a steer in 3 days 500 mg/kg signs of acute tox. in 3 days (steer).	Rowe, V.K. and Hymas, T.A.: Amer. J. Vet. Res. 15:622, 1954
1957	1. Report that chloracne caused by TCDD - definitive. 2. First report of chloracne in 2,4,5-T workers specifically. (non-accident situation). Suggestion that it may be due to dioxin impurity.	Kimmig, J. and Schulz, K.: Dermatologica 115:540, 1957.
1959	Suggested synthetic pathway for dioxin production in the 2,4,5-T process.	Tomita, M. et al. Yakugaku Zasshi 79: 186, 1959
1964	Porphyria Butanea Tarda reported in 2,4-D and 2,4,5-T workers.	Bleiberg, J. et al.: Arch. Derm. 89:793, 1964.
1964	Toxicity to domestic animals a) liver degeneration in cattle	Palmer, J.S. and Radeleff, R.D., Ann. N.Y. Acad. Sci. 111:729-736, 1964.

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<u>Date</u>	<u>Effects Observed/Comments</u>	<u>Reference</u>
1964	With an increase in the demand for 2,4,5-T, Dow Chemical changes its production techniques to increase yield. Result was an outbreak (60 workers) of chloracne.	Panel on Herbicides, 1970
1965	Dow identifies chloracne problem in 2,4,5,-T workers as TCDD contamination. Standardizes methods of detection and informs other manufacturers. Technology for limiting TCDD contamination to no more than 1 ppm now exists.	Panel on Herbicides, 1970
1966	Dow builds new 2,4,5-T facility designed to limit TCDD contamination.	Panel on Herbicides, 1970
1967	National Cancer Institute (NCI) study from Bionetics Research Laboratory evaluated the carcinogenic and teratogenic potential of 2,4,5-T which was later shown to contain 27 ppm TCDD. Reported 2,4,5-T to be teratogenic in mice, embryotoxic in rats at relatively high doses. These studies were questioned because of: 1. abnormal variations in procedure 2. small numbers of animals used 3. teratogenicity and embryo-lethality in controls 4. animal strains used were inappropriate 5. no common skeletal malformations were found in controls 6. known teratogens did not cause significant teratogenic responses.	Panel on Herbicides, 1970
1969	2,4,5-T production stopped at Nitro, West Virginia plant.	Monsanto World Hdqts. News 24(3), 1980
~1970	Dow teratology study with 2,4,5-T (with low TCDD contamination) showed 2,4,5-T to be non-teratogenic in rats at doses of 1,3,6,12 and 24 mg/kg/day.	Panel on Herbicide, 1970

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Date	Effects Observed/Comments	Reference
1970	National Institute of Environmental Health Sciences produced studies with 2,4,5-T containing varying amounts of dioxin. Concluded 2,4,5-T to be teratogenic in mice regardless of dioxin content, but rats showed a teratogenic response more related to the dioxin levels of the samples used.	Panel on Herbicides, 1970
1970	2,4,5-T production stopped at the Krummerich plant; Sauget, Illinois.	Monsanto World Hdqts. News 24(3), 1980
1972	Human neural tube defects reported in offspring of New Zealand 2,4,5-T workers.	Sare, W.M. and Forbes, P.I.: New Zealand Med. J. 75:37-38, 1972
1974	Subchronic and chronic studies in rodents with 2,4,5-T. 1. Increased liver weight 2. Increased liver glycogen 3. No enzyme effects 4. positive effects completely reversible	Chang, H., et al.: J. Agr. Food Chem. 22:62-65, 1974 (supported by subsequent studies)
1975	Suggestion of possible mutagenic activity - human chromosome effects. 1. single chromatid breaks 2. sample had significant TCDD contamination	Fujita, K., et al. J. Jpn. Assoc. Rural Med. 24:77-79, 1975
1975	Behavioral effects in rodents reported. 1. maze learning inhibited	Sjoden, P.O. and Soderberg, V.: Physiol. Psychol. 3:175-178, 1975
1976	Chronic studies in rodents: 1. thymus atrophy 2. splenic atrophy 3. hypocellularity of bone marrow and lymph nodes	Highman, B., et al.: J. Toxicol. Environ. Hlth. 1:469-484, 1976
1976	Acute dosing in rodents. 1. renal organic acid transport mechanisms affected	Koschier, F.J. and Berndt, W.O.: Toxicol. Appl. Pharmacol. 37:169; 38:297-306, 1976

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Date	Effects Observed/Comments	Reference
1979	Alsea, Oregon epidemiological study on increased incidence of spontaneous abortion. 1. attributed to periods of heavy 2,4,5-T use	EPA: Environ. Sci. and Tech. 13:640-641, 1979
1980	a) Mortality/carcinogenicity epidemiological study of Nitro plant workers exposed in 1949 accident. 1. no excess death or excess cancer death b) Study on Dow 2,4,5-T workers. 1. no excess death or excess cancer death.	a) Zack, J.A. and Suskind, R.R.: J. Occ. Med. 1:4, 1980 b) Ott, M.G., et al.: J. Occ. Med. 22: 47-50, 1980
1982	Completion of morbidity study of Nitro plant workers exposed to 2,4,5-T process (including accident exposed persons).	Suskind, R.R., et al.: in review.

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September 29, 1983

Dr. Allan T. Ford
Mail Code A1SE
Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

Dear Al:

I am interested in analyzing the works and writings of all experts who will be used by plaintiffs in the Nitro case. As you would anticipate, I am starting with Carnow and Coneybear. May I ask if you could supply me with the biographies and bibliographies of each? I would like to have a list of materials written by either or both and, to the extent possible, copies of the actual articles. Please let me have these as soon as possible. If Monsanto has not made a formal literature search then please request author searches of both from Jan Williams with hard copies of all writings for us. I would be most appreciative of your help in this.

As usual, I have a second issue to cover at the same time.

In "Fate of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in the Environment: Summary and Decontamination Recommendations," the authors (Young, Thalken, Arnold, Cupello and Cockerham, 1976) discuss hepatic ultrastructure studies (cf. page 27 et seq.). The inference made by the authors of this report is that ingestion of TCDD do not cause structural or steric effects on the endoplasmic reticulum. I would appreciate it if you would review this against your knowledge of effects of TCDD on hepatocellular ultrastructure and intracellular organelles and tell me if you agree with the inference I have drawn. Can we conclude that TCDD has no effect on the endoplasmic reticulum? What other references support your conclusions? What is known about effects of TCDD on cellular organelles in the intact mammal?

I would appreciate your help in both of these areas.

Very truly yours,


WEINBERG CONSULTING GROUP Inc.
Myron S. Weinberg, Ph.D.

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MONSANTO POLYMER PRODUCTS CO.
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October 13, 1983

Dr. Myron Weinberg
Weinberg Consulting Group, Inc.
Suite 301
2828 Pennsylvania Avenue, N.W.
Washington, DC 20007

Dear Myron:

In answer to your September 29 letter, I have completed literature searches on most but not all of the expert witnesses who are to testify for the plaintiffs in the Nitro litigation. I will xerox and send the 8" stack to you late this week or early next week, but I need to organize and find out what is missing first. I have run a few of the "experts" through LEXIS/NEXIS with poor results. I believe that there is more in the media domain than I am seeing. Do you know of an alternate source for covering the media area? Perhaps our lawyers can do more with the legal data base.

In terms of getting hard copy of the abstracted papers, do you think that I should give these papers priority over the TCDD literature? I seem to be taxing both the DMEH and R&D libraries at the moment, and the expert witness literature looks to contain hundreds of articles. However, I can stop and move in this direction if necessary.

On your second question: "can we conclude that TCDD has no effect on the endoplasmic reticulum?", I do not think that the Young inference is real as there are indications to the contrary in the literature. I discussed the matter with Dr. Knutson of Poland's staff this week, and she indicated that with acute or chronic exposure, there is a progressive thickening or swelling of the endoplasmic reticulum - the end result of which I am not sure about but will do some looking. It is interesting that Knutson indicated that she did not know of any study of the long-term effects or the ramifications in terms of toxicity.

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Dr. Myron Weinberg

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October 13, 1983

I have enclosed the articles from the last batch of abstracts you sent us. We are still finding less than 20% of the toxicological papers which indicates the inherent weakness in our data base. We have begun entering new papers as fast as we can get folders made up, key words assigned, and computer input completed. We expect to have another 250 papers this week and possibly 400 next week. I have sent you a computer printout of the data base as it existed early last week.

I am looking forward to seeing you next Monday. I will be staying at the Guest Quarters just down the street from your office.

Sincerely,



A. M. Ford, PhD.

Enclosures

cc: T. Bistline
C. Love
G. Griffin
F. E. Kearney
W. McCarville

P.S. - I have enclosed a book of the process chemistry involved in the various Nitro processes. This book is considered very confidential to Monsanto Company, and we would like it returned at the end of the litigation.

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