Origins of Human Cancer

BOOK C
Human Risk Assessment

edited by
H. H. Hiatt
Harvard School of Public Health

J. D. Watson
Cold Spring Harbor Laboratory

J. A. Winsten
Harvard School of Public Health

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Copied by MCA for distribution to the Vinyl Chloride Technical Panel and Research Coordinators, April 17, 1978, Mr. J. T. Seawell

Abstracts of Papers for the Seventeenth Annual Meeting of the Society of Toxicology, San Francisco, California March 12–16, 1978

246. *The Effect of Disulfiram on Vinyl Chloride-Induced Carcinogenesis in Mice.* J. M. WINSTON, J. C. BHANDARI, A. M. EL-HAWARI, R. D. SHORT, JR., and C. C. LEE, Pharmacology-Toxicology, Midwest Research Institute, Kansas City, Missouri.

Male and female CD-1 mice were exposed to 50, 250, or 1000 ppm of vinyl chloride (VC) 6 hr/day, 5 days/week for 49 weeks. To determine the effect of disulfiram (DS) on VC-induced carcinogenesis, one-half of the mice received 0.1% DS in the daily diet for the duration of the study. Bronchiolo-alveolar adenomas were found in all mice exposed to 1000 ppm of VC both with and without DS treatment. However, the tumors tended to occur at a later time in the DS-treated mice. The incidence of hepatic hemangiosarcoma in the mice exposed to 1000 ppm of VC was less in the mice treated with DS than mice without DS treatment. The incidence of mammary gland tumors in females exposed to 1000 ppm of VC was also reduced with DS treatment. In mice exposed to 250 ppm of VC, the incidence of bronchiolo-alveolar adenoma was not affected by DS treatment. The incidence of hepatic hemangiosarcoma in 250-ppm VC exposed mice was reduced by DS treatment. Studies of the activity of hepatic mixed function oxidase enzymes showed DS treatment to reduce the activity. DS plus VC resulted in a partial decrease in activity. These data suggest that chronic DS treatment may produce at least partial protection against VC-induced carcinogenesis and that the effect of DS on mixed-function oxidase activity may be involved in this protective effect. (Supported by Contract No. NIEHS-N01-ES-2-2084.)

Recd. 11-19 → JPL Here we go again. 11-21
Rec. fax to Mond, P+PD + Poly U (re TRI, butadiene - TDI) to ask if they are prepared to undertake necessary effort within deadlines. Also fax to J. Ashley for info.

CHEMICAL MANUFACTURERS ASSOCIATION

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File CMA

November 10, 1986

TO: HEALTH AND SAFETY CONTACTS OF CMA MEMBER COMPANIES

FROM: Nancy G. Doerrer
Manager, Health, Safety and Chemical Regulations

SUBJECT: IARC's Classification of Potential Chemical Carcinogens: March 1987 Monograph Meetings

As part of a chemical industry initiative to promote the development and application of sound scientific principles, CMA requests your continued participation in the 1986-1987 IARC Monograph program.

BACKGROUND

The Chemical Manufacturers Association has been invited to nominate an observer to participate in two upcoming meetings of the International Agency for Research on Cancer (IARC).

Since July 1986, many of you have assisted CMA in evaluating key industrial chemicals in preparation for IARC Monograph meetings to be held 2-9 December 1986 in Lyon, France. At that time a working group of experts chosen by IARC will assess the activity of approximately 200 chemicals/exposures in short-term tests. Dale W. Matheson, Ph.D., of Stauffer Chemical Company will attend the December meeting as the official CMA Observer. Richard H. McKee, Ph.D., of Exxon Biomedical Sciences, Inc., will serve as the Alternate. Final preparations for the December meeting are well underway.

At a second meeting, to be held 10-17 March 1986 in Lyon, the degrees of evidence for carcinogenicity in humans and experimental animals will be assessed for the 200 chemicals/exposures. An overall evaluation of carcinogenic risk to humans will then be made based on experimental and epidemiological data. The list of chemicals/exposures is attached for your review (Attachment 1). These substances have previously been evaluated by IARC in Volumes 1-41 of the Monographs, but are now undergoing a second review.

OLI 3482

INDUSTRY PARTICIPATION

The CMA Health and Safety Committee's IARC Work Group is organizing industry participation in the March 1987 meeting. The number of chemicals and short time period for assessment of this list has dictated a method of action that requires full CMA member company participation. The following schedule has been constructed to prepare for effective scientific input at this important meeting:

DEADLINE: DECEMBER 1, 1986

- Identify chemicals/exposures on the list (Attachment 1) that are of specific concern to your company.

- Identify company expert(s) to assess the health effects literature and evaluate the carcinogenic data on chemicals of concern to your company. Return the attached form (Attachment 2) to CMA by December 1, 1986.

- Nominate the CMA Observer to attend the March 1987 IARC Monograph meetings. The CMA Observer will not have a vote at the upcoming Monograph meetings, but will have the opportunity to contribute to discussions concerning the scientific evidence for classifying chemicals as carcinogens. The nomination of this observer will consist of careful selection from a list of names generated by representatives of CMA member companies. The CMA IARC Work Group encourages you to suggest potential nominees. H. Vainio, M.D., Chief of IARC's Unit of Carcinogen Evaluation and Identification, has requested that CMA submit the name of the industry observer to IARC by 31 December 1986.

DEADLINE: DECEMBER 15, 1986

- Submit to CMA a bibliography of recently published animal and epidemiological information relevant to the carcinogenic assessment of chemicals of concern to your company. (Dr. Vainio recently made this specific request in a letter to CMA of 29 October 1986. By "recently published," we interpret Dr. Vainio's request to mean relevant articles published since the IARC Monograph in question was issued.)

DEADLINE: JANUARY 14, 1987

- Submit to CMA an executive summary (using the format outlined in Attachment 3) describing IARC's assessment of the chemical/exposure in question, your assessment, and a full bibliography, including unpublished studies.

A logical method for arriving at the conclusions in your executive summary is as follows:

Begin your review by locating the appropriate IARC Monograph(s) in which the original IARC carcinogenicity evaluation was described. By referring to the cumulative index at the back of the latest volume of the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, you will easily access the appropriate Monograph(s).

Next, identify IARC's conclusions on a given chemical's carcinogenic potential. These conclusions will be expressed as "degrees of evidence" for carcinogenicity from studies in humans, in experimental animals, and from short-term tests. An overall evaluation of carcinogenic risk to humans may have been made for chemicals assessed in Volumes 1-29. These evaluations appear in Supplement 4 of the IARC Monographs (October 1982) as classifications into Groups 1, 2a, 2b or 3. (Refer to the "Preamble" to each Monograph for an explanation of the "degrees of evidence" and the groupings.)

CMA suggests that you review the appropriate IARC Monograph for accurate interpretation and inclusion of relevant information. Identify instances where you believe IARC may have misinterpreted the evidence. Secondly, identify key information not considered by IARC, i.e. data that was overlooked at the time of consideration by the IARC Committee and/or new information that has been developed since the Monograph was published.

CMA contends that published and unpublished data should be reviewed in IARC evaluations. IARC's policy is to consider only published information; nevertheless, this policy does not preclude the chemical industry from including valid, high quality industrial test data in our written submission of chemical reviews to IARC. In the event that you find key information that is new to the IARC carcinogen evaluation, consider submitting the data for publication to a peer-reviewed journal or some other written public forum. Taking this step assures that the data will be officially considered by the IARC Committee.

Although it may be unrealistic to expect reclassifications for chemicals in Group 1, it is nevertheless important to review any new or unpublished information previously unavailable to the IARC Working Groups.

At the March 1987 meetings, IARC will make "... evaluations of the degrees of evidence for carcinogenicity in humans and experimental animals ... for these chemicals and exposures and an overall evaluation of carcinogenic risk to humans will be made based on experimental and epidemiological data." To assist you in making your own evaluation, CMA suggests that you review two papers:

a) Review and Recommendations for the Revision of the Preamble and Criteria of the IARC Monographs, CMA/AIHC/API/NACA/PMA, July, 1986 (recently sent to you under separate cover).

b) Criteria for Identifying and Classifying Carcinogens, Mutagens and Teratogens, CMA/SOCMA/CEFIC/CCPA. In press, Reg. Toxicol. Pharmacol., December 1986.

Please contact me if you need copies of either of these documents.

Finally, write an executive summary on your findings, and include a full bibliography. Retain your file of collected articles, manuscripts or other forms of information at your office for future reference by the CMA IARC Work Group and the CMA Observer.

CMA anticipates that in your executive summaries you will divulge no confidential information. If such information is included, please designate it with a CBI notation.

* * * * * * * *

CMA recognizes that there may be significant overlap in company interests in a given chemical. When we receive your list of chemicals and names of company experts, we will put you in touch with other member companies who have expressed the same interest so that you may equitably distribute the task of literature searching and carcinogen evaluation.

<u>If you are interested in having your company's chemicals represented at the March 1987 IARC Monograph meetings, please make every effort to meet the deadlines cited in this memo.</u>

I can be reached at 202/887-1282 with your questions or comments. I look forward to hearing from you.

Attachments

cc: IARC PROJECT PARTICIPANTS: December 1986 IARC Monograph Meetings
CMA Health and Safety Committee

ATTACHMENT 1

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: CHEMICALS AND INDUSTRIAL PROCESSES ASSOCIATED WITH CANCER IN HUMANS: UPDATING OF SUPPLEMENT 4 (PART I & PART II)

TENTATIVE LIST OF SUBSTANCES AND EXPOSURES TO BE CONSIDERED

(At IARC Monograph Meetings December 2-9, 1986, and March 10-17, 1987)

Exposure
Acetaldehyde
Acrolein
Acrylonitrile
Actinomycin D
Adriamycin
Aflatoxins
Aldrin
Aluminium production
4-Aminobiphenyl
Amitrole
Anaesthetics, volatile
Analgesic mixtures containing phenacetin Phenacetin
Aniline (and its hydrochloride)
Arsenic and arsenic compounds
Asbestos
Attapulgite
Auramine, manufacture of Auramine
Azathioprine
Benzene
Benzidine
Benzidine-based dyes: Direct Black 38 Direct Blue 6 Direct Brown 95
Beryllium and beryllium compounds
Betel quid with and without tobacco (chewing) Betel leaf Areca nut
N,N'-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)
Bischloroethyl nitrosourea (BCNU)
Bis(chloromethyl)ether and technical-grade chloromethyl methyl ether
Bitumens
Bleomycins
Boot and shoe manufacture and repair
Bracken fern
1,3-Butadiene
1,4-Butanediol dimethanesulphonate (Myleran)
Cadmium and cadmium compounds
Carbon blacks
Carbon tetrachloride
Carpentry and joinery
Chemotherapy for lymphomas: MOPP, etc.
Chlorambucil
Chloramphenicol
Chlordane/Heptachlor

OLI 3486

Exposure

Chlorinated toluenes, production of:
- Benzal chloride
- Benzotrichloride
- Benzoyl chloride
- Benzyl chloride

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)

Chloroform

Chlorophenols
- 2,4-Dichlorophenol
- Pentachlorophenol
- 2,3,4,6-Tetrachlorophenol
- 2,4,5-Trichlorophenol
- 2,4,6-Trichlorophenol

Chloroprene

Cholesterol

Chromium and chromium compounds

ortho-Chrysoidine

Cisplatin

Clofibrate

Coal gasification

Coal-tar pitches

Coal-tars

Cok production

Creosotes

Cyclamates

Cyclophosphamide

Dacarbazine

Dapsone

DDT

Diazepam

1,2-Dibromo-3-chloropropane

Exposure

ortho-Dichlorobenzene and para-Dichlorobenzene

3,3'-Dichlorobenzidine

Dichloromethane

1,3-Dichloropropene

Dieldrin

Diethyl sulphate

3,3'-Dimethoxybenzidine (ortho-Dianisidine)

Dimethylcarbamoyl chloride

Dimethyl sulphate

1,4-Dioxane

Epichlorohydrin

Erionite

Ethylene dib· mide

Ethylene oxide

Ethylene thiourea

Fluorides (inorganic, in drinking-water)

5-Fluorouracil

Formaldehyde

Furniture and cabinet making

Haematite mining, underground (with exposures to radon)
Haematite (iron oxide)

Hexachlorobenzene

Hexachlorocyclohexane

Hydralazine

Hydrazine

Iron and steel founding

Exposure

Iron dextran complex

Isonicotinic acid hydrazide

Isopropyl alcohol manufacture
(strong-acid process)
Isopropyl alcohol
Isopropyl oils

Lead and lead compounds

Leather dusts

Leather goods manufacture

Leather tanning and processing

Lumber and sawmill industry

Magenta, manufacture of
Magenta

Melphalan

6-Mercaptopurine

Methotrexate

5-Methoxypsoralen (+ UVR)

6-Methoxypsoralen (+ UVR)

Methyl bromide

4,4'-Methylene bis(2-chloroaniline)
(MOCA)

4,4'-Methylene bis(2-methylaniline)

N-Methyl-N'-nitro-N-nitrosoguanidine

Metronidazole

Mineral oils

Mustard gas

1-Naphthylamine

2-Naphthylamine

1-Naphthylthiourea

Exposure

Nickel r fining
Nickel and nickel compounds

Nitrogen mustard

Ochratoxin A

Oxymetholone

Phenazopyridine (and its
hydrochloride)

Phenelzine

Phenobarbital

Phenoxyacid herbicides
2,4-D and esters
2,4-DP
MCPA
MCPP
Silvex
2,4,5-T and esters

Phenylbutazone

N-Phenyl-2-naphthylamine

Phenytoin

Polybrominated biphenyls

Polychlorinated biphenyls

Prednisone

Procarbazine hydrochloride

Propylene oxide

Propylthiouracil

Pulp and paper manufacture

Reserpine

Rubber industry

Saccharin

Sepiolite

Exposur

Sex hormones:
- Combined oral contraceptives
- Sequential oral contraceptives
- Other oestrogen-progestin combinations

Androgens:
- Testosterone

Oestrogens:
- Chlorotrianisene
- Conjugated oestrogens
- Dienoestrol
- Diethylstilboestrol
  - Diethylstilboestrol dipropionate
- Ethinyloestradiol
- Hexoestrol
- Mestranol
- Oestradiol-17β and esters
- Oestriol
- Oestrone and oestrone benzoate

Progestins:
- Chlormadinone acetate
- Dimethisterone
- Ethynodiol diacetate
- 17α-Hydroxyprogesterone caproate
- Lynoestrenol
- Medroxyprogesterone acetate
- Megestrol acetate
- Norethisterone
  - Norethisterone acetate
- Norethynodrel
- Norgestrel
- Progesterone

Other:
- Clomiphene
  - Clomiphene citrate

Shal -oils

Silica

Smokeless tobacco products

Soots (and soot extracts)

Spironolactone

Styrene

Sulfafurazole

Sulfamethoxazole

Talc

Exposure

Tetrachlorodibenzo-*para*-dioxin (TCDD)

1,1,2,2-Tetrachloroethane

Tetrachloroethylene

Tobacco smoke

2,4- and 2,6-Toluene diisocyanates

ortho-Toluidine

Treosulphan

Trichloroethylene

4,5',8-Trimethylpsoralen (+ UVR)

Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)

Tris(1-aziridinyl) phosphine sulphide (Thiotepa)

Uracil mustard

Vinblastine sulphate

Vincristine sulphate

Vinyl chloride

Vinylidene chloride

Wollastonite

Wood dusts