Answers To Questions On The Issuance Of An Emergency Temporary Standard For Certain Chemicals Considered To Be Carcinogens B-179768

Occupational Safety and Health Administration
Department of Labor

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

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The Honorable Bill Archer, House of Representatives
The Honorable M. Caldwell Butler, House of Representatives
The Honorable George A. Goodling, House of Representatives
The Honorable James F. Hastings, House of Representatives
The Honorable G. V. Montgomery, House of Representatives
The Honorable Steven D. Symms, House of Representatives
The Honorable Joe D. Waggoner, House of Representatives
The Honorable Antonio Borja Won Pat, House of Representatives

Gentlemen:

In accordance with your September 24, 1973, request and subsequent discussions with your offices, we are reporting on

--the Occupational Safety and Health Administration's (OSHA's) basis for issuing an emergency temporary standard for 14 chemicals considered to be carcinogens, particularly MOCA--a trade name used by E. I. du Pont de Nemours and Company for the chemical 4,4'-Methylene-bis(2-chloroaniline),

--the adequacy of safeguards provided by the Occupational Safety and Health Act of 1970 to protect the individual's right of due process after a standard has been promulgated,

--our evaluation of OSHA's decision relating to issuing the standard, and

--the possible waste of public funds if OSHA lacked sufficient data to support the issuance of the standard.

As agreed with your offices, we are preparing a separate report on OSHA's issuance of an emergency temporary standard on pesticides, which we expect to issue shortly.

Appendixes II, III, and IV were copied directly from OSHA or National Institute for Occupational Safety and Health (NIOSH) documents and should not be considered as our views or as facts we developed.

We interviewed OSHA officials, reviewed OSHA files and records relating to issuing the standard, and considered the adequacy of safeguards provided by the Occupational Safety and Health Act of 1970 to protect the individual's right of due process. We also interviewed officials of NIOSH regarding their role in issuing the standard.

As requested, we did not obtain formal OSHA comments. The report contents, however, were discussed with OSHA officials and their comments were considered in preparing the report.

We do not plan to distribute this report further unless any of you agree or publicly announce its contents.

Sincerely yours,

Elmer B. Staats

Comptroller General
of the United States

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APPENDIX I

ANSWERS TO QUESTIONS ON THE ISSUANCE OF

AN EMERGENCY TEMPORARY STANDARD FOR

CERTAIN CHEMICALS CONSIDERED TO BE CARCINOGENS

INTRODUCTION

In December 1970 the Congress enacted the Occupational Safety and Health Act of 1970 (29 U.S.C. 651). One reason for this legislation was concern about occupational exposure to carcinogens.

Section 6(c)(1) of the act states that the Secretary of Labor shall provide, without regard to the requirements of chapter 5, title 5, of the United States Code (administrative procedures), for an emergency temporary standard to take immediate effect upon publication in the Federal Register if he determines that

--employees are exposed to grave danger from substances or agents determined to be toxic or physically harmful or from new hazards and

--such a standard is necessary to protect employees from the danger.

On May 3, 1973, an emergency temporary standard to regulate employee exposure to 14 chemicals considered to be carcinogens was published in the Federal Register. The standard was revised on July 27, 1973, to provide more definitive controls for workplaces and work operations and to require more explicit warning signs and container labels. The events before this standard was issued are summarized as follows.

On May 23, 1972, the Occupational Safety and Health Administration (OSHA) requested the National Institute for Occupational Safety and Health (NIOSH) to obtain information on nine chemicals alleged to be carcinogenic. NIOSH, in a preliminary report to OSHA on July 14, 1972, listed 15 substances as chemical carcinogens, which included the 9 identified on OSHA's request, and recommended that a permit system to control carcinogens in the workplace be considered.

Such a system would have required each employer that manufactured, distributed, or operated a process involving any of the chemicals to apply to OSHA for a use permit based on the safeguards to be used by the employer to protect the workers.

The 15 substances on the NIOSH list were (1) 2-Acetylaminofluorene, (2) 4-Aminodiphenyl, (3) Benzidine (and its salts), (4) 3,3'-Dichlorobenzidine (and its salts), (5) 4-Dimethylaminoazobenzene, (6) alpha-Naphthylamine, (7) beta-Naphthylamine, (8) 4-Nitrobiphenyl, (9) N-Nitrosodimethylamine, (10) beta-Propiolactone, (11) bis-Chloromethyl ether, (12) Methyl Chloromethyl ether, (13) 4,4'-Methylene-bis (2-chloroaniline), (14) Ethylenеimine, and (15) Dimethyl Sulfate.

On December 29, 1972, the Health Research Group and the Oil, Chemical, and Atomic Workers International Union petitioned OSHA to establish an emergency temporary standard regulating exposure of employees to 10 substances alleged to be carcinogens. On February 9, 1973, OSHA published a notice of receipt of the petition in the Federal Register and requested interested persons to comment on the petition before March 11, 1973. OSHA received written comments from about 50 manufacturers, trade associations, labor unions, medical research laboratories, and other interested parties.

On April 26, 1973, the Assistant Secretary for Occupational Safety and Health determined that

--14 of the 15 chemicals (Dimethyl Sulfate was deleted because of questionable evidence) were toxic and physically harmful,

--exposure to any of the 14 chemicals posed a grave danger to employees,

--employees were being exposed to the substances, and

--an emergency temporary standard was necessary to protect them.

According to OSHA officials, OSHA preferred a uniform work practice standard over the use-permit system recommended by NIOSH because (1) there were some unresolved

questions on whether the act would have permitted OSHA to adopt a use-permit system instead of a uniform work practice standard, (2) implementing a use-permit system would have required OSHA to evaluate many different applications on a case-by-case basis, possibly causing serious administrative problems, and (3) OSHA wanted to avoid any legal or administrative problems or delays in protecting workers from the substances.

SCIENTIFIC AND ECONOMIC DATA SUPPORTING THE ISSUANCE OF THE STANDARD

NIOSH's initial report to OSHA in July 1972 implicated each of the 14 chemicals as a carcinogen. Before the emergency temporary standard was issued, NIOSH made available to OSHA additional information on these 14 chemicals; this information was formalized and subsequently transmitted to OSHA as "hazard reviews."

These "hazard reviews," which are summaries of available scientific literature, show that each of the 14 chemicals has produced tumors in two or more different species of animals, indicating a potential carcinogenic nature. (See app. II for OSHA's summary of the NIOSH hazard reviews.) Also OSHA prepared an environmental impact statement on the standard which states that 6 of the 14 chemicals have been proven through epidemiological studies to be carcinogenic to humans.

The problems of environmental exposures to chemical agents and the scientific criteria for evaluating carcinogenic hazards were discussed in an April 1970 report to the Surgeon General by the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens. In part, the report states (1) "Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man" and (2) "No level of exposure to a chemical carcinogen should be considered toxicologically insignificant for man. For carcinogenic agents 'a safe level for man' cannot be established by application of our present knowledge."

APPENDIX I

In response to our request, the Director of OSHA's Office of Standards provided the following statement regarding the medical, technical, and economic data used to justify issuing the temporary standard on carcinogens.

> "Both emergency standards [carcinogen and pesticide] were promulgated pursuant to Section 6(c) of the OSH Act without substantial technical or economic data. In each instant (sic) it was determined that employees were exposed to grave danger and that the standards were necessary to protect employees.
>
> "The extent of danger from exposure to carcinogens and pesticides remains unknown. For carcinogens, medical science has not determined dose-response relationships, possible latency periods or metabolites for certain of these substances including MOCA. Each of the carcinogens have been demonstrated to produce cancer in two or more different species of animals. NIOSH has advised us that exposure of humans to such substances poses a risk that such exposure will produce cancer. Public hearings (held after the issuance of the emergency temporary standard) have failed to produce clinically significant evidence that a latent carcinogenic danger does not exist for each substance covered by the emergency temporary standard. OSHA concluded that there was insufficient medical, technical and economic data to justify the risk of continued exposure of workers to potentially carcinogenic substances."

In addition, OSHA's environmental impact statement contains the following information on the use of the 14 chemicals and on the number of employees and employers affected by the standard:

> "Only seven of the carcinogens are currently produced in commercial quantities and the remainder are presently used only for research or appear as contaminants of some other chemicals. Most of these latter seven were commercially produced at one time, but have fallen into non-use since they have been proven to be human carcinogens.

> "* * * approximately 250 firms with about 1,200 employees are known to be affected by the proposed regulations. It is estimated that the number of firms is closer to 1,700 and the number of employees exposed is closer to 12,000, with over 80 percent of these working with 4,4'-methylene-bis (2-chloroaniline)."

The effect of many toxic substances on humans is almost immediate with readily observable symptoms; however, the carcinogenic effect of most cancer-producing agents is not observable until months or years after exposure. Though it is not yet known whether a single exposure to such substances is sufficient to cause cancer, it is known that usually a long latency period between the initial exposure and the development of cancer occurs. On the basis of animal experiments and epidemiological studies available to OSHA and the criteria provided by the Surgeon General's Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens, all 14 chemicals could be carcinogenic to man. We believe that OSHA was justified in initiating action to safeguard workers exposed to the 14 chemicals.

CARCINOGENICITY OF 4,4'-METHYLENE-BIS (2-CHLOROANILINE)--MOCA

MOCA was developed in the early 1950s as the best of several chemicals which could be used to manufacture elastomeric articles. Elastomers are synthetic rubber or plastic substances having some of the properties of natural rubber. Large-scale commercial production began about 1962. MOCA has since become a commercially important curing agent. (See app. III for selected extracts on MOCA taken from OSHA's environmental impact statement.)

The animal experimentation data on MOCA indicates its potential carcinogenic nature. For example, the NIOSH hazard review on MOCA states that the results of the studies involving rats and mice as reported by three independent groups of investigators clearly demonstrate an active oncogenic (tending to cause tumors) role for MOCA. The review further states that the absence of definitive industrial experience and the positive findings in two animal studies by three independent investigators preclude the elimination of MOCA as a human carcinogen.

In these two studies, tumors developed not only in the liver but in the lungs. The NIOSH hazard review states that this finding appears significant since the rat is not particularly sensitive to lung cancer. (See app. IV for NIOSH's hazard review on MOCA.)

On the basis of the animal evidence cited by NIOSH and the criteria provided by the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens, MOCA could be carcinogenic to man.

SAFEGUARDS TO PROTECT THE INDIVIDUAL'S RIGHT OF DUE PROCESS AFTER PROMULGATION OF STANDARDS

The Occupational Safety and Health Act of 1970 includes several provisions to safeguard the individual's right of due process once a standard has been promulgated. These provisions allow (1) any affected employer to apply to the Secretary of Labor for a variance from a standard, (2) any person adversely affected by a standard to challenge its validity by filing a petition with the U.S. court of appeals within 60 days after a standard is promulgated, (3) an employer to contest a citation or proposed assessment of penalty for violating a standard, and (4) any employee or employee representative to file a notice with the Secretary challenging the reasonableness of the time fixed in a citation for abating a violation.

Variance from a standard

Subsection 6(b)(6)(A) of the act states that "any employer may apply to the Secretary for a temporary order granting a variance from a standard or any provision thereof promulgated under this section." A temporary order may be granted to the employer if he cannot comply with a standard by its effective date and establishes that (1) professional or technical personnel or materials and equipment needed to comply with the standard are unavailable or necessary construction or alteration of facilities cannot be completed, (2) he is taking all available steps to safeguard his employees against the hazard covered by the standard, and (3) he has an effective program for complying with the standard as quickly as possible. This subsection also states that a temporary order may be granted only after

notice has been given to employees and an opportunity provided for a hearing; the Secretary may issue one interim order until a decision is made on the basis of the hearing.

Section 6(d) of the act states that "any affected employer may apply to the Secretary for a rule or order for a variance from a standard promulgated under this section." Such a variance can be granted when an employer can show that he does or will provide working conditions as safe and healthful as would result if he complied with the standard.

As of November 1973, OSHA had received 12 variance applications regarding the emergency temporary standard on carcinogens. An OSHA official stated that

--the revised emergency temporary standard issued on July 27, 1973, eliminated the need for variances in five of the applications and these cases were closed;

--for two of the remaining variance applications, the applicants--Allied Chemical Corporation and Polyurethane Manufacturers Association--were granted interim orders;

--the five remaining applications were not being processed because the emergency temporary standard had expired but that action would be taken on these applications, if necessary, when the permanent standard on carcinogens was issued.

Petition for judicial review

Section 6(f) of the act states that any person who may be adversely affected by a standard issued under section 6 may at any time before the 60th day after such standard is promulgated file a petition challenging the validity of the standard with a U.S. court of appeals.

Several interested parties filed petitions in May and June 1973 with the U.S. Court of Appeals for the Third Circuit. The petitions challenged the inclusion of two substances--3,3'-Dichlorobenzidine (DCB) and Ethyleneimine (EI) --in the emergency temporary standard for carcinogens. The petitioners contended that

--the record contained no substantial evidence showing that the use of DCB and EI satisfied the provisions of subsection 6(c)(1) of the act as to conditions necessary to justify the promulgation of an emergency standard,

--the findings of fact and statement of reasons for the standard contained in its preamble were inadequate, and

--the Assistant Secretary violated the National Environmental Policy Act of 1969 by failing to prepare an environmental impact statement before issuing the standard.

The court found the statement of reasons in the standard's preamble insufficient in two respects:

1. The statement failed to set forth the basis for the finding that the 14 chemicals listed in the standard were carcinogens. To satisfy subsection 6(e), the statement should have indicated which data in the record was being principally relied on and why that data sufficed to show that the substances were harmful and posed a grave danger to exposed employees. The court stated that this could have been accomplished by a brief statement in the May 3, 1973, notice that certain scientific data (citing the record documents) showed that DCB and EI produced cancer in rodents and indicated that they were therefore carcinogenic in man.

2. The statement of reasons failed to explain why this standard was "necessary to protect the employees from such exposure." The court stated it did not mean to say that every procedure must be justified as to every substance, type of use, or production technique. The court read subsection 6(e) as requiring at least a general explanation of why the procedures prescribed were chosen in light of the recommendations of scientific experts and other governmental bodies, the types of industrial practices with these chemicals, and the alternative kinds of regulations considered by OSHA.

Because of the deficiencies in the statement of reasons, the emergency temporary standard was vacated as to DCB and EI.

An OSHA official informed us that OSHA had the appropriate documentation on these two substances, but it was not properly set forth in the preamble to the standard.

Regarding the preparation of an environmental impact statement, the court stated that, though the National Environmental Policy Act (NEPA) requirement applies to ordinary standards promulgated under the Occupational Safety and Health Act, an exception should be made for the emergency temporary standard involved in this case. The court also concluded that, when OSHA issues a draft environmental impact statement within a reasonable time after issuing such a standard, the requirements of NEPA are satisfied.

Contesting a citation, a proposed assessment of penalty, or an abatement period to the Occupational Safety and Health Review Commission

In carrying out its enforcement activities, OSHA issues citations to employers and determines penalties to be imposed. The citations must be in writing; describe the nature of the violation; and specify what rule, standard, or order has allegedly been violated. The citation must also give the employer a reasonable time to correct the violation.

Section 10(a) of the act provides that an employer may contest a citation or proposed assessment of penalty within 15 working days after receiving it.

Similarly, employees or employee representatives who wish to challenge the reasonableness of the period specified in a citation for correcting a violation must file a notice with the Secretary within 15 working days following the issuance of the citation.

Whenever an employer files an appropriate notice with the Secretary, the Occupational Safety and Health Review Commission must afford him a hearing. It must also permit affected employees to participate in the review proceedings

whether or not they have filed a notice challenging the period allowed to correct a violation. Similarly, when employees file a timely notice challenging the abatement period, the Commission must afford them a hearing and review, even when the employer has not contested the citation or penalties.

GAO'S EVALUATION OF OSHA'S DECISION TO ISSUE THE STANDARD

We discussed with OSHA officials the basis for their decision to issue an emergency temporary standard on carcinogens. They stated that available scientific evidence on the 14 chemicals necessitated timely action to protect exposed workers rather than take additional time to complete a criteria package to support the promulgation of a permanent standard.

OSHA's decision to issue a temporary standard was based on (1) the scientific evidence available at that time, (2) the criteria provided by the Surgeon General's Ad Hoc Committee on Low Level Environmental Carcinogens, (3) the Health Research Group and the Oil, Chemical, and Atomic Workers' petition requesting the establishment of a temporary standard, and (4) the responses received in regard to the Federal Register notice requesting comments on the petition.

Notwithstanding the court decision to vacate the temporary standard as to DCB and EI, which was based on its findings that OSHA did not appropriately set forth the basis for the standard in the preamble, it appears that OSHA's decision to issue the standard was reasonable.

POSSIBLE WASTE OF PUBLIC FUNDS IF OSHA LACKED SUFFICIENT DATA TO SUPPORT THE ISSUANCE OF THE STANDARD

Because the data available to OSHA appears to have been sufficient to justify issuing the emergency temporary standard, we did not evaluate the expenditure of public funds involved.

APPENDIX II

OSHA'S SUMMARY OF THE 14 NIOSH HAZARD REVIEWS

(1) 2-Acetylaminofluorene

Experimental animal investigations involving rats, mice, rabbits, dogs, hamsters and fowl have demonstrated the carcinogenicity of 2-Acetylaminofluorene (2-AAF). Investigations into the mechanism whereby 2-Acetylaminofluorene exerts its carcinogenic effect have demonstrated that the N-hydroxylated metabolite, N-hydroxy-2-AAF, was produced in several animal species and was more carcinogenic than the parent compound. The National Cancer Institute (NCI) demonstrated that humans also metabolize this substance to the same carcinogenic metabolite. From these findings, it seems reasonable to conclude that 2-AAF, which has been shown to be carcinogenic in many animal species, is carcinogenic in man.

(2) 4-Aminodiphenyl

The potential of 4-Aminodiphenyl (4-ADP) to induce bladder cancer in humans has been established in epidemiologic studies conducted by Melick et al. and Koss et al. Deichmann & Radomski considered 4-ADP to possess a relative carcinogenic potential for the dog 6 times greater than that of beta-Naphthylamine, 17 times greater than that of 4-Nitrobiphenyl and 27 times greater than that of Benzidine. In addition, the carcinogenicity of 4-ADP has been well-established in the open scientific literature with demonstrated potential for malignant tumor induction in rabbits and mice. The accumulated experimental and epidemiologic evidence have demonstrated 4-Aminodiphenyl may be the most hazardous aromatic amine regarding carcinogenic potential.

(3) Benzidine

Benzidine was demonstrated to be carcinogenic in experimental animal investigations involving rats, dogs, hamsters, and mice. Epidemiologic investigations of worker populations exposed to Benzidine have clearly demonstrated that this substance and its salts are also carcinogenic in humans. The incidence of urinary bladder cancer in workers exposed to Benzidine in these epidemiologic investigations greatly exceeded the incidence of this disease in the general population.

(4) 3,3'-Dichlorobenzidine

The determination that 3,3'-Dichlorobenzidine (DCB) is potentially carcinogenic for humans rests on the determination that DCB has been shown to be carcinogenic in controlled animal studies involving rats, mice and hamsters. A clearly defined and statistically significant worker population exposed to DCB only, in either the past or in the present, is difficult to ascertain. Existing worker populations have been either exposed to other listed chemical carcinogens in their past work experience or are presently being exposed to other suspect carcinogens in addition to DCB. Therefore, the cas for the human carcinogenicity of DCB must rely on extrapolation to humans of the most pertinent animal studies of oncogenesis.

The studies by the NCI concerning the induction of tumors, significantly including bladder tumors in hamsters, and the studies by Pliss et al. concerning the induction of tumors in mice and rats present experimental evidence of tumor production in three animal species.

Although DCB has been detected in the urine of workers receiving a minimum of exposure, the metabolism of this substance is unclear, although it probably differs from that of other carcinogenic aromatic amines such as Benzidine and beta-Naphthylamine.

(5) 4-Dimethylaminoazobenzene

Numerous reports concerning carcinogenicity of 4-Dimethylaminoazobenzene (DAB) in experimental animals have been published. This substance was demonstrated to be carcinogenic in rats, dogs, neonatal mice and trout. The similarity in metabolism of various aromatic amines in dogs and humans, emphasizes the importance of the finding that DAB had been demonstrated carcinogenic for dogs.

(6) alpha-Naphthylamine

The contamination of alpha-Naphthylamine (1-NA) by beta-Naphthylamine (2-NA) a potent carcinogen, and mixed occupational exposures involving 1-NA and other aromatic amines has confounded the epidemiologic conclusion that

1-NA is carcinogenic in man. Both 1-NA and 2-NA are readily metabolized to various derivatives, several of which have a demonstrated carcinogenic potential in experimental animals. The demonstration that a metabolite of 1-NA, N-Hydroxy-1-naphthylamine, possessed a greater carcinogenic potential than the corresponding 2-NA metabolite, N-Hydroxy-2-naphthylamine, emphasizes this consideration. In addition, the extensive epidemiologic study in the dyestuffs industry conducted by Case failed to eliminate an active role for 1-NA as a human bladder carcinogen.

(7) beta-Naphthylamine

beta-Naphthylamine (2-NA) was demonstrated to induce cancer of the urinary bladder in dogs, rhesus monkeys and hamsters. Tumors were induced in other organs of rats and mice exposed to 2-NA although attempts at tumor induction in rabbits was unsuccessful. Epidemiologic investigations of worker populations exposed to 2-NA clearly demonstrates that this substance is carcinogenic in humans.

(8) 4-Nitrobiphenyl

Because of the structural similarity of 4-Aminodiphenyl to 4-Nitrobiphenyl and the experimental evidence for in vivo formation of 4-Aminodiphenyl from 4-Nitrobiphenyl, the epidemiologic investigations published by Melict et al. and by Koss et al. are of special significance. These studies have demonstrated the potential of 4-Aminodiphenyl to induce urinary bladder cancer in humans. The case of the carcinogenicity of 4-Nitrobiphenyl is strongly supported by the induction of urinary bladder cancer in dogs, the evidence that 4-Nitrobiphenyl is metabolized, in vivo, to 4-Aminodiphenyl (a highly carcinogenic aromatic amine), and the possibility that the cases of human urinary bladder cancer attributed by Melick et al. to 4-Aminodiphenyl only, may have been induced by exposure to 4-Nitrobiphenyl as well.

(9) N-Nitrosodimethylamine

The carcinogenicity of N-Nitrosodimethylamine (DMN) for the liver and kidney of the rat has been repeatedly demonstrated in experimental studies. In addition, primary tumors

of the lungs have been induced in rats administered oral doses of DMN and inhalation of DMN has produced tumors of the nasal area. Other experimental animal investigations have demonstrated the carcinogenicity of DMN for the mouse, the hamster, the guinea pig, the rabbit and several species of fish. In view of this broad spectrum of carcinogenic activity in experimental animals, DMN must be regarded as potentially carcinogenic for man.

(10) beta-Propiolactone

The carcinogenicity of beta-Propiolactone (BPL) has been demonstrated in mice by skin application, subcutaneous injection and intraperitoneal injection. Malignant tumors have been induced in rats by subcutaneous injection, intratracheal administration, and intragastric feeding. Skin application to hamsters induced a very high incidence of skin tumors. Although epidemiologic evidence demonstrating BPL to possess a carcinogenic potential for humans is not available, the weight of the experimental animal data indicates that BPL is also a carcinogen in humans.

(11) bis(Chloromethyl) ether

Investigations with experimental animals (mice and rats) have demonstrated that bis(Chloromethyl) ether (BCME) is a very hazardous carcinogenic substance. Skin application or subcutaneous injection of experimental animals has resulted in malignant lesions at the site of application or injection and in malignant tumors of the lungs. Of significance was the demonstration that 1 ppm or 0.1 ppm of BCME in air, induced lung cancer in mice or rats. Epidemiologic investigations conducted separately by the National Institute for Occupational Safety and Health and others demonstrated that employee exposure to BCME is extremely hazardous with a high probability of lung cancer.

(12) Chloromethyl Methyl ether

The results of investigations with experimental animals exposed to commercial grades of Chloromethyl methyl ether (CMME) have been inconclusive regarding the carcinogenicity of this substance because of contamination by small concen-

trations of the highly carcinogenic bis- derivative-bis (Chloromethyl)ether. However, experimental animal investigations involving chemically purified CMME have demonstrated that this substance possesses a carcinogenic potential.

Epidemiologic investigations reported in 1972 and 1973 strongly implicated CMME as a human carcinogen, although concomitant exposure to BCME cannot be discounted.

(13) 4,4'-Methylene-bis(2-chloroaniline)

The results of experimental animal studies involving rats and mice, as reported by three different groups of investigators, have clearly demonstrated a carcinogenic potential for 4,4'-Methylene-bis (2-chloroaniline). The results of two industrial studies involving workers exposed to 4,4'-Methylene-bis(2-chloroaniline) were not definitive and cannot be relied upon to assess the hazards of occupational exposure to this substance, although one of the studies reported that several exposed workers developed hematuria.

(14) Ethyleneimine

The carcinogenic potential of ethyleneimine (EI) has been confirmed by a study conducted by Walpole in 1954 involving rats and one sponsored by the National Cancer Institute involving mice. In the first study, animals developed injection site sarcomas which the investigators attributed to the direct action of Ethyleneimine, and in the second study 80 percent of the animals developed tumors, including more than one-half with hepatomas (which the investigators stated had "malignant potentiality") and almost three-quarters with pulmonary tumors. Although high doses of EI were administered, the investigators stated there was no way to predict whether man would be more or less susceptible to tumor induction by EI.

The case for the carcinogenicity of EI, then, rests on the extrapolation to humans of the findings in two separate, controlled animal studies. This position is compatible with that of NIOSH concerning the prior demonstration of carcinogenicity in at least two animal studies.

APPENDIX III

SELECTED EXTRACTS ON MOCA AS TAKEN FROM

OSHA'S ENVIRONMENTAL IMPACT STATEMENT

Trade Names

"MOCA" (DuPont)
"L D-813" (DuPont-liquid)
"Curene 442" (Anderson Development Company)
"Cyanaset M" (American Cyanamid)

Synonyms

3,3'-Dichloro-4,4'-diaminodiphenylmethane
4,4'-methylene bis (2-chloroaniline), methylene-bis-ortho-chloroaniline

Description

Yellow to light gray-tan pellets which melt at approximately 220°F. Also available in liquid form. This compound shows the general toxicity characteristics common to aromatic amines and may produce cyanosis* if ingested. It is a proven carcinogen in rats.

Source

The three major manufacturers of 4,4'-methylene (bis)-2-chloroaniline are DuPont, Anderson Development Company and Nixon and Cox (United Kingdom). The major suppliers in the United States are DuPont, Anderson Development, and American Cyanamid.

Quantities Produced

Estimated U.S. production during 1972:

solid pellets	4.7 million lbs.
liquid	2.0 million lbs.
export sales (solid)	.6 million lbs.
Estimated total	7.3 million lbs.

*Cyanosis is a bluish or purplish discoloration of the skin due to deficient oxygenation of the blood.

U.S. sales in 1972 were in excess of 8.7 million dollars.

Number of Employees Potentially Exposed

It is impossible to develop a precise estimate of the number of employees exposed since:

a) the number of firms involved is large and the firms vary in size and type of operation
b) most firms have not yet reported their use of the chemical as required under subsection (e) of the Emergency Temporary Standard (38 FR 1092a)

Thirty-eight firms have reported a total of 382 employees potentially exposed.

Based on the data currently available, between 2,000 and 25,000 employees are estimated to be exposed to this substance, with a best guess of approximately 10,000.

Uses

DuPont describes "MOCA" as a hindered, aromatic diamine which:

-has good vulcanizate properties and a convenient working life with liquid urethane elastomers.
-provides a curing system for liquid urethane polymer blends
-is an effective curing agent for epoxy resins.

"MOCA" has three characteristics which account for its broad use: 1. It melts at a convenient temperature (212-228° F) 2. It has a reactivity rate which permits adequate mixing time with liquid polymers before setting, and 3. It provides an unusually good mix of desirable physical properties in the final products.

The major use of "MOCA" is to produce approximately 32 million pounds of solid elastomeric parts (approximately 14% "MOCA").

A smaller quantity (in liquid form) is used to produce approximately 150 million pounds of cross-linked urethane foam, as is used in automotive seating and dashboard safety pads.

Users

Between 800 and 1,800 firms use this compound to manufacture a large variety of products. Users include many small firms as well as some of the largest firms in the United States. The Office of Standards has specifically identified approximately 120 users of 4,4'-methylene (bis)-2-chloroaniline.

DuPont response to the Draft Environmental Impact Statement of May 3, 1973 identifies specific uses and users of "MOCA," including the following:

1. Military

Ball seals on nuclear submarines, underwater listening device encapsulation, Navy warship gun mounts, protection of jet engine turbine blades, protective covers for equipment in radar systems, and components of nuclear weapons.

2. Industrial

Rollers used in the steel fabricating and plywood industries, components in home appliances such as washing machines and dryers, automobile components, wheels for forklift trucks, urethane shoe soles, and many others.

3. Specific firms

Several firms were identified that would be significantly impacted by the unavailability of "MOCA" cured parts.

a) Ford facilities for the production of off-the-road equipment could be shut down 20-30 weeks while developing alternate engineering and retooling.

b) Polaroid, Xerox, IBM and Eastman Kodak utilize small rollers and drive belts in cameras, computers, and reproduction equipment.

c) Boeing Vertol uses "MOCA" urethane dies for helicopter part metal foaming.

Cost of Compliance

A preliminary estimate indicates that the equipment necessary to completely enclose and automate a typical operation (production of solid elastomeric parts) is available for less than $15,000.* (A major supplier is considering modification of his shipping container so that material can be transferred from the container to this type of system without requiring an employee to completely open the container).

A firm reporting under subsection (e) of the Emergency Temporary Standard has stated that they have applied for a Small Business Administration loan to meet the cost of a new manufacturing facility. Loans of this type are specifically provided for in the Occupational Safety and Health Act of 1970.

The Polyurethane Manufacturers Association stated in May 1973 that approximately 40 small firms have discontinued their operations involving 4,4'-methylene (bis)-2-chloroaniline. Many of these firms stopped their activities because of confusion over exactly what was required for compliance with the Emergency Temporary Standard. It is anticipated that most (if not all) of these firms will resume their activities in light of the Revision of Emergency Temporary Standard (38 FR 20074, July 27, 1973) and the grant of an Interim Order with respect to the Polyurethane Manufacturers Association request for a variance (38 FR 20127, July 27, 1973).

Comments

Developed in the early 1950's, "MOCA" was the best of several chemicals which could be used to manufacture strong, durable oil resistant, resilient elastomeric articles by simple liquid casting. Because of its desirable characteristics, "MOCA" came into wide use. However, the industry also became aware of its toxic nature, and of its proven carcinogenicity in animals. The major manufacturers have

*Estimate based on cost of "Flying Wedge," "Quick Melt," and "Vacuum Transfer" available from Advanced Machine Planning, Inc.

spent in excess of a million dollars in trying to find a general substitute for "MOCA." However, the substances tested have turned out to be expensive, or equally toxic, or do not have the same mix of desirable characteristics. For example, an alternative to "MOCA" in some applications is 3,3' dichlorobenzidine, another carcinogen.

A cost push price increase can be expected for "MOCA" and for "MOCA" end-product items. The trend toward increased use of "MOCA" because of its ease of use will probably diminish where substitutes are available and acceptable. Since many "MOCA" users are relatively small (in terms of capital and facilities), it is probable that increased cost of raw material and costs of employee protection will result in some business shut-downs.

APPENDIX IV

NIOSH'S HAZARD REVIEW OF MOCA

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

A preliminary report concerning the carcinogenicity of orally introduced 4,4'-methylene-bis(2-chloroaniline)* in rats was made by Steinhoff and Grundmann [1] in 1969. In 1970 these two investigators published a more extensive paper [2] of their completed findings. In the later paper the toxicity and carcinogenicity of 4,4'-methylene-bis(2-chloroaniline) was compared with that of 4,4'-diaminodiphenylmethane (DDM). Both of these compounds are used as hardeners or curing agents for epoxy resin systems and isocyanate-containing polymers. [2, 4, 7] Although commercial production of 4,4'-methylene-bis(2-chloroaniline) began in 1962, [3] DDM has been in production for over 25 years. [4] The investigators quote previous work to document the strong toxic effect of DDM on both rat and human liver as well as the carcinogenic effect on rat liver. Schoental [4] has also demonstrated the carcinogenicity of DDM on the rat liver. An accidental acute poisoning episode occured in 1965 in Great Britain in which 84 persons became ill, some seriously, with jaundice following the consumption of bread accidentally contaminated with DDM. [5] In general, Steinhoff and Grundmann [1 and 2] considered 4,4'-methylene-bis(2-chloroaniline) to be less toxic but more carcinogenic than the non-chlorinated compound, DDM.

In their experiments Steinhoff and Grundmann [1 and 2] maintained fifty 100-day-old Wistar rats (25 male; 25 female) on a low protein diet containing 0.1 percent 4,4'-methylene-bis(2-chloroaniline) for 500 days. (Acute toxicity tests had earlier demonstrated the relative nontoxicity of the compound when all ten experimental animals in the study survived either an oral or a subcutaneous administration of a single dose of 5000 mg/Kg.) Control rats used in the chronic feeding experiment were maintained on an identical low protein diet excluding the test compound. At the termination of the 500-day experimental feeding period (total dose of 27 g/Kg body weight) the experimental animals were maintained on the

*4,4'-methylene-bis(2-chloroaniline)or 3,3'-dichloro-4,4'-diaminodiphenylmethane has been given the registered trademark, MOCA, by the E. I. du Pont de Nemours & Co., Inc.

ntrol diet. The average life span for male rats was 565 test days, the average for females was 535 test days. The average life span for controls was 730 test days.

Of the 25 male animals, 23 died with tumors. Twenty-two animals had liver tumors and in 7 of these, primary lung tumors (not metastases) occurred also. Two of the animals with liver tumors had lung metastases and one brain metastasy was observed. One animal without liver tumors exhibited "massive tumor permeation" of the lungs and benign bladder papillomas were observed in one animal. The two tumor-free animals exhibited fatty livers with isolated necrosis and hemorrhages.

Of the 25 female animals, 20 died with tumors. Eighteen animals had liver tumors and in 4 of these animals, three also had primary lung tumors (not metastases) and one had mammary gland tumors. Two animals had lung tumors without liver tumors and 9 had benign mammary gland tumors. The investigators emphasized that lung tumors in rats are relatively rare. Of the 50 control animals only two mammary fibroadenomas were observed in female rats, although the average life span of the controls was longer than that of the experimentals.

In another set of experiments Steinhoff and Grundmann [6] injected a suspension of 94 percent pure, technical grade 4,4'-methylene-bis(2-chloroaniline) into 34 Wistar rats (17 males, 17 females). Subcutaneous injections of 500 or 1000 mg/Kg body weight were administered on the order of once a week, or at longer intervals, to a total dose of 25 g/Kg body weight. Twenty-two of the 34 animals died with a total of 29 malignant tumors. Nine animals had liver cell carcinomas which, in all but one such animal, were discovered in multiple locations. Primary lung carcinomas were formed in 7 animals with a multi-central distribution in 3 animals. In the 50 control animals (25 males, 25 females) a total of 13 malignant tumors at different sites were discovered, including one lung tumor. No liver tumors developed over an average life span of 1040 days compared to an average life span of 778 days in experimentals. The investigators stated:

"Thus, 3,3'-dichloro-4,4'-diaminodiphenylmethane exhibits a definite carcinogenic action in the rat, the liver and lungs being the main organs affected, even after subcutaneous administration and sufficient protein nutrition. However, a greater number of liver tumors appear in a shorter time after feeding the compound in a low-protein diet."

In 1972, Sherman and Zapp [7] presented investigations in which rats fed a normal diet, but containing 1000 ppm of 4,4'-methylene-bis(2-chloroaniline), for 18 months subsequently developed lung tumors with some spreading to the pleural cavity. The investigators also observed an increased incidence of liver tumors. When animals were maintained on a low protein diet containing the compound, the incidence and malignancy of both liver tumors (males) and mammary tumors (females) was found to increase.

A contemporary paper by the National Cancer Institute reports on the work of the Weisburgers [8] concerning the carcinogenicity of 4,4'-methylene-bis(2-chloroaniline) in mice and rats. Preliminary studies established the maximally tolerated dose of this compound in the diet was 1000 mg/Kg body weight in rats and 2000 mg/Kg body weight in mice. Control animals were maintained on Purina laboratory chow during the chronic feeding investigations while equal numbers of experimental animals (25 male mice; 25 female mice; 25 male rats) were dosed at the above levels and other groups at half these levels. Tumors observed in experimental animals and absent in controls included: hepatomas in rats (4/19 effective rats at the high dose and 1/22 effective at the low dose) 1 glioma; 2 adenocarcinomas of the lung; 2 gastrointestinal adenocarcinomas; 1 ear duct tumor; 2 tumors of the urinary bladder; and 7 adenomata of the lung.

In female mice, hepatomas were observed in 50 percent of the animals at the high dose and 43 percent at the low dose. No hepatomas were observed in female control mice. In male mice there was no significant difference between experimentals and controls concerning the incidence of hepatomas. Although no vascular tumors (hemangiomas and hemangiosarcomas) were found in control mice, such tumors

were observed in 40 percent of the males and 43 percent of the females receiving the high dose. At the low dose 23 percent of the males and none of the females were observed to develop vascular tumors. Malignant lymphomas which were common in control mice were not as common in the experimental animals.

It is interesting that three independent studies [6 through 8] have reported the development of lung tumors in rats exposed to 4,4'-methylene-bis(2-chloroaniline). As emphasized by the investigators of two of these studies, [6 and 8] the rat is not highly susceptible to lung tumor formation. The influence of diet is known to alter the carcinogenic potential of various substances and diet apparently affects the carcinogenic potential of 4,4'-methylene-bis(2-chloroaniline), but the results of two studies [7 and 8] in which the experimental animals were maintained on a normal diet, to which the test substance was added, clearly demonstrate that the effect of diet, alone, is not sufficient to account for the oncogenic activity of 4-4'-methylene-bis(2-chloroaniline).

A single plant cohort study involving a group of 31 employees and an equal number of controls was published by Linch et al [3] in 1971. The length of exposure of the control group was not specified. When compared to the control group no significant findings were observed utilizing the Pap technique as a screening tool for the early identification of bladder cancer.

Medical records for 178 employees were reviewed for evidence of acute illnesses, specific systemic illnesses, chronic disease, and malignancy. With the exception of 4 individuals all individuals in this group had not been exposed to 4,4'-methylene-bis(2-chloroaniline) for the last 10 years. In this group the elapsed time since first exposure was:

a)	less than 10 years	- no employees
b)	from 10 to 15 years	- 158 employees
c)	more than 15 years	- 20 employees

If the assumption is made that, of the group of 158 employees, 15 years had elapsed since the first exposure, and that no exposure had occurred for 10 years, then their total exposure

was 5 years. Likewise, the total exposure of the group of 20 employees in which more than 15 years had elapsed since first exposure would be a maximum of approximately 2 years. Because of the short exposure durations of both groups, it should not be considered unusual that negative findings were reported since the known average latency period for development of occupational bladder cancer is approximately 20 years.

The fact that the rate of cancer deaths in the plant population was better than national cancer statistics is not surprising when consideration is given to the differences between the total U.S. population and the able working population of the plant.

These investigators considered the principal route of absorption to be other than respiratory and recommended biologic rather than air monitoring as the procedure of choice for exposure control.

Another industrial study involved the finding by Mastromatteo[9]in 1965 that two of six employees, both in their thirties, who had a mixed exposure to 4,4'-methylene-bis(2-chloroaniline), TDI and several isocyanate-containing resins developed urinary frequency with hematuria in addition to eye irritation, respiratory irritation with cough and tightness in the chest. The hematuria can best be related to the 4,4'-methylene-bis(2-chloroaniline) than to the other substances. The author considered the conditions to be mild but also considered that exposure to this substance, primarily by dust inhalation, was the cause of the observed cystitis.

The results of the experimental animal studies involving rats and mice, as reported by three independent groups of investigators, [1,2,6,8] clearly demonstrate an active oncogenic role for 4,4'-methylene-bis(2-chloroaniline).

The absence of definitive industrial experience with only 2 reported studies, [3 and 9] and the positive findings in two animal studies by 3 independent investigators, preclude the elimination of 4,4'-methylene-bis(2-chloroaniline) as a human carcinogen.

APPENDIX IV

References for 4,4'-methylene-bis(2-chloroaniline)

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