PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.
I. SUMMARY

In December, 1980, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation at Sandoz Colors and Chemicals, East Hanover, New Jersey. The request concerned exposure to 6-acetoxy-2,4-dimethyl-m-dioxane (DMD), which is used as an antimicrobial agent in the preparation of some colors at the plant. This chemical is commonly sold under the brand names Dioxin(TM) and Dimethoxane(TM). It should not be confused with the herbicide contaminant, "dioxin" (2,3,7,8-tetrachloro-dibenzo-p-dioxin). DMD has been shown to be carcinogenic in animal studies and has been selected by the National Testing Program for carcinogenesis bioassay (1980).

The antimicrobial agent (DMD) is supplied to Sandoz in aqueous solution and is added to an aqueous solution of the colors in the mixing of pigments. In an aqueous solution, DMD hydrolyzes to form acetic acid, acetaldehyde and 3-hydroxybutyraldehyde. This last substance is in equilibrium with crotonaldehyde. None of these substances are known to be carcinogenic. Of these substances, crotonaldehyde is the most hazardous. Since NIOSH has no sampling and analytical method for DMD, it was decided to survey for crotonaldehyde as an indicator of the concentration of DMD. No standard for exposure to DMD has been established or recommended by any governmental agency.

On March 4, 1982, a survey was performed at the operations where the maximum exposure to DMD would occur, namely where DMD is added to the raw chemicals and where it is used in the mixing of the pigments. The exposures to crotonaldehyde in the mixing department were less than half of the Permissible Exposure Limit of 6 milligrams per cubic meter of air, established by the Occupational Safety and Health Administration (OSHA).

Based on the findings of the survey, NIOSH considers that no hazard from exposure to the hydrolysis products of DMD exists. The presence of the hydrolysis products of DMD indicates that some exposure to DMD is probable. Because of the question of carcinogenic potential of DMD, NIOSH recommends that mixing vessel lids be closed and that exhaust ventilation be used whenever possible. The company should continue to investigate the possible replacement of DMD with a less toxic antimicrobial agent.

KEYWORDS: SIC 2816 (Colors and Pigments); Dimethoxane(TM), Dioxin(TM), 6-acetoxy-2,4-dimethyl-m-dioxane (DMD), acetic acid, acetaldehyde, 3-hydroxybutyraldehyde, crotonaldehyde, carcinogenicity.
II. INTRODUCTION

In December, 1980, the National Institute for Occupational Safety and Health (NIOSH) received a request to perform a health hazard evaluation for exposure to DMD, an antimicrobial agent, at Sandoz Color and Chemicals, East Hanover, New Jersey. NIOSH representatives visited the plant on January 20, 1981 and performed a walk-through survey of the areas where colors and dyes were used. This is a non-union plant. Therefore, representative workers from the various sections of the plant were interviewed about their use of DMD and were informed of the purpose of NIOSH's visit.

III. BACKGROUND

This facility is located on a large "campus". Most of the buildings are offices or research/testing laboratories. The only "industrial" activity on the campus is the mixing of aqueous dispersions of pigments or dyes. The antimicrobial agent, DMD, is used in the mixing of pigments, but not of dyes. The greatest exposure to DMD occurs in the mixing department. To some extent, laboratory personnel who use the pigments are exposed to DMD and/or its hydrolysis products.

The mixing operation takes place in a two story building. The mixing area on the second floor is approximately 60' x 60' with a 15 feet high ceiling. The first floor, which contains the mixing vats and packaging operation, is of approximately the same dimensions. The work force is made up of 3 operators and one technician per shift. There are ten mixing vats, whose capacities range from 850 to 3,600 gallons (7,000 to 30,000 pounds of liquid). Normally, three to five vats are in operation at any one time, processing one to five batches. Three to five days are required to process one batch. The ingredients of a batch consist of pigment, water, an anionic surfactant and the antimicrobial agent (DMD), (6-acetoxv-2,4dimethyl-m-dioxane) known by the brand names Dimethoxane and Dioxin. About two pounds of DMD is added to 1000 pounds of water. Yearly consumption of DMD is between 1,500 and 2,000 pounds.
At the start of a mixing operation, the pigment, surfactant and DMD are weighed and added to a vat which is being filled with water. The DMD is supplied to the company in 55 gallon drums as a 92% solution in water. About two minutes are required to tap the drum, manually weigh the solution and add it to the vat. The pigment mixture in the vat is aerated and churned for a few days until it meets the company's specifications. Although heat is not applied to the mixture, heat evolved by mixing the solution elevates the temperature somewhat above room temperature. The openings at the tops of the vats are fitted with lids, however it is common practice to keep most of the lids open during the operation. Three of the vats are fitted with exhaust ventilation. There is good dilution ventilation on the second floor, provided by a bank of windows. Some of the operators commented on occasional slight eye irritation. There is an occasional perceptible sweet odor, such as that of acetaldehyde, in the area. DMD has a mustard-like odor. When the pigment mixture meets the company's specifications, it is piped into 55 gallon drums. The drumming operations are located on the ground floor. During the processing, a batch of color is transferred from vat to vat, as needed. After each batch is processed, the vats are flushed with water until clean of the color which had been processed.

The operators' duties involve weighing the ingredients, filling the vats, transferal of batches between vats, observation of the process, obtaining samples for testing, and piping product into drums. There are no permanent work stations, and the operators move about the area during the work day. The normal work shifts are 7 AM to 3:30 PM and 3 PM to 11 PM.

IV. EVALUATION DESIGN AND METHODS

DMD is widely used as a preservative against spoilage microorganisms such as bacteria, fungi and yeasts in aqueous systems and emulsions. In addition to pigments, it is used as a preservative with cutting oils, paints, cosmetics and inks.

DMD is purchased in a water solution and is added to a large quantity of water in the process. DMD (6-acetoxy-2,4-dimethyl-m-dioxane) hydrolyzes in water to produce equimolar quantities of 3-hydroxybutyraldehyde, acetaldehyde and acetic acid (C₂H₄O₂ + H₂O ↔ C₄H₈O₂ + C₂H₄O + C₂H₄O₂). Hydrolysis is not instantaneous, therefore some DMD may be assumed to be present in the mixture. On the day of sampling, one batch was approximately 1/2 day old, another batch was started in the afternoon. As the boiling point of acetaldehyde is near room temperature, the reaction tends toward completion. In aqueous solution, the 3-hydroxybutyraldehyde is in equilibrium with crotonaldehyde (CH₃CH(OH)CH₂CHO ⇌ CH₃CH=CHCHO + H₂O).
There are no standards established for exposure to DMD and no sampling and analytical method for airborne DMD has been developed by NIOSH. Due to the fact that DMD hydrolyzes, a sampling/analytical method for airborne DMD would be tenuous. Therefore, it was decided to sample and analyze for one of the hydrolysis products, crotonaldehyde. The samples were collected in midget impingers at a sampling rate of 1 or 1.5 liters per minute for 2 or 3 hours, using 10 milliliters of a 1% sodium bisulfite (NaHSO₃) solution as the collection media and were analyzed by a standard method using gas chromatography with flame ionization detection. In theory, crotonaldehyde reacts with the sodium bisulfite to force the equilibrium statement (3-hydroxybutyraldehyde $\rightarrow$ crotonaldehyde) to crotonaldehyde. One mole of DMD would produce one mole of crotonaldehyde. The concentration of crotonaldehyde could therefore be used to estimate the potential concentrations of airborne acetaldehyde and acetic acid. By inference, the amount of DMD needed to produce the hydrolysis products can also be estimated.

As the sampling media was liquid, and a possible loss of liquid could occur due to body movement, it was decided to collect most of the samples in fixed locations in the mixing department near the dye vats. The concentrations measured in these samples probably overestimate employees' exposures, as the employees move about during the day. Two samplers were worn as "personal samples" by NIOSH's industrial hygienist. These samples, also, may overestimate exposures, as the industrial hygienist tended to observe the operations and remain near the mixing vats.

V. EVALUATION CRITERIA

Crotonaldehyde

The odor of crotonaldehyde is reported to be pungent and irritating. Exposure to crotonaldehyde may cause irritation of the eyes, nose, throat and skin and respiratory passages. Exposure may also result in difficulty in breathing which may occur several hours following exposure¹. The Occupational Safety and Health Administration (OSHA) has established a Permissible Exposure Limit (PEL) of 2 parts per million parts of air (ppm) or 6 milligrams per cubic meter (mg/M³) for crotonaldehyde². The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted the same concentration as their time weighted average (TWA)³. The ACGIH also has adopted a short term exposure limit (STEL) for crotonaldehyde of 6 ppm or 18 mg/M³. The ACGIH limits were adopted to prevent irritation of the eyes and respiratory passages.
Acetic Acid

Dilute acetic acid is and smells like vinegar. Exposure to the vapors of acetic acid may cause irritation of the eyes, mucous membranes, skin and lungs. Delayed breathing difficulties may occur. Contact of the skin or eyes with concentrated acetic acid may cause severe damage. Outward signs of repeated or prolonged exposure to acetic acid may include a darkening of the skin and erosion of exposed front teeth. These effects would not be expected from exposure to the low concentrations found at this plant. Both the OSHA PEL and the ACGIH TWA for exposure to acetic acid are 10 ppm or 25 mg/M³. The ACGIH STEL is 15 ppm or 37 mg/M³.

Acetaldehyde

Acetaldehyde has a penetrating, fruity odor (the odor in the mixing department was sweet). Exposure to acetaldehyde vapor may cause irritation of the eyes, nose and throat. Inhalation of high concentrations of acetaldehyde vapor may cause drowsiness and dizziness. Contact of the eye with liquid acetaldehyde may cause burning and irritation. An allergic skin rash may result from repeated exposure to acetaldehyde. Volunteers exposed to 200 ppm of acetaldehyde for a few minutes developed transient conjunctivitis. Exposure to even 50 ppm may produce mild eye irritation. The OSHA PEL for exposure to acetaldehyde is 200 ppm or 360 mg/M³. The ACGIH TWA is 100 ppm or 180 mg/M³, with a STEL of 150 ppm or 270 mg/M³.

3-Hydroxybutyraldehyde

There are few reports in the literature on 3-hydroxybutyraldehyde (also known as aldol). It is reported in the Registry of Toxic Effects of Chemical Substances (RTECS) as being mildly irritating to the skin of test animals. Another reference states that the irritating effects of 3-hydroxybutyraldehyde are likely attributable to crotonaldehyde. "Dangerous Properties of Industrial Chemicals" lists aldol as being a moderate irritant. No exposure limits for 3-hydroxybutyraldehyde have been established or recommended.

Dimethoxane (DMD), (6-acetoxy-2,4-dimethyl-m-dioxane)

Part of the concern which generated this health hazard evaluation request stems from the confusion of the antimicrobial agent (DMD) (6-acetoxy-2,4-dimethyl-m-dioxane), commonly known by the trade names Dimethoxane and Dioxin, with "dioxin" (2,3,7,8-tetrachloro-dibenzo-p-dioxin), which is best known as a highly toxic contaminant of the herbicide, Agent Orange. The toxicological effects of exposure to the two compounds are not related. Exposure to the herbicide contaminant "dioxin" may produce chloracne, impaired liver function, gastro-intestinal irritation, depression and irritation of the central nervous system and possible birth defects.
Until about ten years ago, DMD was considered to have low toxicity and it still is widely used for the control of microorganisms in aqueous solutions and emulsions. In 1974, DMD was tested for carcinogenic activity by being fed (as a 1% aqueous solution) to test animals (rats). Fourteen tumors developed in the 25 test animals as compared with one in the 14 control rats. DMD has been selected by the National Testing Program for carcinogenesis assay (1980). The results of that assay are not yet available.

Sensitization to DMD in a cream vehicle has been reported. The report of an investigation of a textile worker who had developed allergic contact dermatitis to DMD demonstrated that the individual had become sensitized to acetaldehyde and crotonaldehyde, not to DMD. RTECS4 does not contain any carcinogenesis or mutagenesis citations for the hydrolysis products of DMD. The positive citations are limited to skin and inhalation irritation studies. The reasons for the reported differences in oncogenic activity between DMD in water solution and its hydrolysis products are not known.

VI. RESULTS AND DISCUSSION

Table I lists the results of the analysis of the samples collected to determine concentrations of airborne crotonaldehyde in the mixing department. The highest concentration measured was approximately 3 mg/M³, about 1/2 the PEL or TWA. The average of the general air (fixed location) samples was 1.6 mg/M³. The average of the personal samples was 2.0 mg/M³.

It should be remembered that the sampling/analytical method used would convert any 3-hydroxybutyaldehyde present in the samples to crotonaldehyde and that the concentration of crotonaldehyde reported may, in fact, represent an airborne crotonaldehyde/3-hydroxybutyaldehyde mixture.

A concentration of 3 mg/M³ of crotonaldehyde represents an equivalent of 0.043 millimoles per cubic meter of air. The hydrolysis of DMD produces equimolar amounts of acetic acid acetaldehyde and 3-hydroxybutyaldehyde (which is in equilibrium with crotonaldehyde). As the vapor pressures of crotonaldehyde (30 mm) and acetic acid (11 mm) are similar, it can be assumed that the airborne molar concentration of acetic acid would be about 0.043 millimoles or 2.6 mg/M³.
The boiling point of acetaldehyde (69°F) is approximately that of room temperature. It can be assumed that all the acetaldehyde hydrolyzed would become airborne. The sampling and analytical methods employed to determine the concentration of crotonaldehyde would, to a lesser extent, also detect the presence of acetaldehyde. No acetaldehyde was reported to be present upon analysis. A possible explanation for this may be that the greater volatility and lesser vapor density of acetaldehyde would tend to enable the small amount of acetaldehyde vapors produced to be diluted more quickly than the other hydrolysis products.

Because the hydrolysis of DMD to acetic acid, acetaldehyde, 3-hydroxybutyraldehyde (and crotonaldehyde) is not instantaneous, it must be assumed that some exposure to DMD occurs. If one assumed that the hydrolysis of DMD was rather slow and that all the crotonaldehyde determined upon analysis derived from the initial presence of airborne DMD, 0.043 millimoles of DMD would correspond to an airborne concentration of 7.5 mg/m³ of DMD. The hydrolysis of DMD is reported to be "rapid" so the airborne concentration of DMD must be assumed to be far less. The vapor pressure of DMD (and 3-hydroxybutyraldehyde) are not reported. The boiling points of crotonaldehyde (216°F), acetic acid (244°F), DMD (186°F) and 3-hydroxybutyraldehyde (181°F) are all rather high. Compounds with high boiling points tend to have low vapor pressures, so one can assume that the vaporization of DMD is similar to that of acetic acid, crotonaldehyde and 3-hydroxybutyraldehyde.

The overall exposure to DMD and/or its hydrolysis products also is a function of the amount of pigment (which contains DMD) produced versus the amount of dye (which does not contain DMD). Current production of pigment is approximately 30 to 40% of total production. Therefore, overall exposure to DMD and/or its hydrolysis products would be less than the concentrations reflected in this survey, which was conducted during the mixing of pigment.

VII. RECOMMENDATION

Exposure to the hydrolysis products of DMD are within acceptable limits. Even though airborne concentrations of DMD could not be measured, it must be assumed that some exposure to DMD does exist, since hydrolysis is not instantaneous. As the carcinogenic potential of DMD and/or the hydrolysis products has not been clarified, it would be prudent to limit that exposure. NIOSH recommends that the covers of the mixing vats be closed as much as possible, and that the three vats with exhaust ventilation be used whenever practical.

The company currently is investigating possible alternative antimicrobial agents for use in their pigments. The use of alternative (and presumably safer) agents should be expedited.
VIII. REFERENCES


3. American Conference of Governmental Industrial Hygienists, Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1981, Cincinnati, Ohio: ACGIH, 1981.


IX. AUTHORSHIP AND ACKNOWLEDGEMENT

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NIOSH/Region II

Originating Office: Hazard Evaluations and Technical Assistance Branch
Division of Surveillance. Hazard Evaluations and Field Studies
Copies of this report are currently available upon request from NIOSH, Division of Standards Development and Technology Transfer, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Center (NTIS), 5285 Port Royal Road, Springfield, Va. 22161. Information regarding its availability through NTIS can be obtained from the NIOSH Publications Office at the Cincinnati address.

Copies of this report have been sent to:

1. The requestor
2. Sandoz Colors and Chemicals, East Hanover, N.J.
5. N.J. State Dept. of Health, Trenton, N.J.

For the purposes of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.
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OSHA Permissible Exposure Limit = 6 mg/M³

nd = none detected. Limit of detection corresponds to approximately 1 mg/M³.