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METABOLIC PRECURSORS OF A KNOWN HUMAN CARCINOGEN, BETA-NAPHTHYLAMINE

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The National Institute for Occupational Safety and Health (NIOSH) has recently learned that both N-phenyl-β-naphthylamine (a widely used rubber antioxidant) and 2-nitronaphthalene (a by-product of α-naphthylamine production) are metabolized to the known human carcinogen, β-naphthylamine. This Bulletin emphasizes the potential problem of the metabolic conversion of materials believed to be relatively innocuous into known human carcinogens.

PHENYL-BETA-NAPHTHYLAMINE

In an October 8, 1976 letter to NIOSH, The B. F. Goodrich Company reported findings indicating that phenyl-β-naphthylamine (PBNA) is metabolized to β-naphthylamine (BNA) by the human body. This confirms an earlier study by Shell Nederland (T.Soc.Geneesk., 53:415-19, 1975).

PBNA was developed as a replacement chemical for BNA when, in the late 1940's, an association was shown to exist between BNA and human bladder cancer. It should be noted, however, that commercial PBNA is contaminated with 20-30 parts per million BNA.

In recent years, there have been three major domestic manufacturers of PBNA. E. I. du Pont de Nemours and Company manufactured PBNA at Deepwater, New Jersey, until December 1975. The only known current domestic producers of PBNA are The B. F. Goodrich Company at Akron, Ohio and Uniroyal, Inc., at Naugatuck, Connecticut. Total domestic production

of PBNA was 4.9 million pounds in 1973, 3 million in 1974, and 1.5 million in 1975.

Most of the phenyl-β-naphthylamine manufactured today is used as an antioxidant in rubber where it can comprise as much as 1% of the finished product. It can also find use as an antioxidant for greases and oils, as a stabilizer during the manufacture of synthetic rubber, and as an intermediate in the synthesis of dyes as well as other antioxidants. NIOSH estimates that 15,000 workers are potentially exposed to PBNA during its manufacture and use. The majority of these exposures are found among rubber fabricators.

Due to the wide use of PBNA in the rubber industry and its structural similarity to BNA, Shell Nederland studied the metabolism of PBNA. This study included four process operators with occupational exposure (by inhalation) to PBNA, along with 19 volunteers who each ingested 10 mg PBNA. Subsequently, one of these volunteers ingested an additional 30 mg PBNA. BNA measured in 24-hour urine samples was in excess of the quantity that would be expected as an impurity of the ingested PBNA. For the volunteers who consumed 10 mg PBNA (contaminated with 0.008 µg BNA), 0.4 to 3 µg BNA was found in their urine. The process operators, estimated to have inhaled 40 mg PBNA (contaminated with 0.032 µg BNA), were found to have 3 to 8 µg BNA in their urine samples.

As a confirmation of Shell's findings, B. F. Goodrich found 3 to 4 µg BNA in 24-hour urine samples from two volunteers who ingested 50 mg PBNA (containing 0.7 µg BNA) and from workers (unspecified number) estimated to have inhaled 30 mg PBNA. These findings, like the Shell study, indicate that phenyl-β-naphthylamine is at least partially metabolized by the human body to β-naphthylamine.

The acute and chronic toxicity of PBNA has been demonstrated in laboratory animals, however, its toxic effects in man are virtually unknown. An epidemiologic study, involving deaths among workers who entered the rubber industry after 1949 (when BNA was replaced by PBNA), shows no significant excess risk of bladder tumors in the industry when compared to the general population. The authors point out, however, that their data is not conclusive (Brit.J.Ind.Med., 31:140-51, 1974).

In addition to the studies demonstrating that PBNA is metabolized to BNA in humans, evidence has been presented which indicates that PBNA is also metabolized to BNA in dogs. At the Imperial Chemical Industries Laboratory in Manchester, England, radioactive PBNA was fed to dogs and radioactive BNA was found in collected urine.

The carcinogenic potential of PBNA in laboratory animals has undergone limited evaluation. In a study involving three female dogs (fed 540 mg

PBNA per day over a period of years), no bladder tumors were seen after 4.5 years. The investigators point out that the relatively few years of exposure to PBNA limits interpretation of these data (Proc.9thInt. Cong.Ind.Med., Budapest, 1948).

In a limited number of laboratory mice fed PBNA for 18 months, the incidence of hepatomas, when compared with controls, was significantly greater than expected. Other laboratory mice, given a single subcutaneous injection of PBNA, showed an increase in the total number of tumors when compared with controls; however, in this group, the incidence of site-specific tumors was not significantly greater than expected (National Cancer Institute, Aug. 1968).

2-NITRONAPHTHALENE

On August 19, 1976, E. I. du Pont de Nemours and Company informed NIOSH of unpublished studies regarding the carcinogenic potential and the metabolism of 2-nitronaphthalene in dogs. This compound (an unmarketed by-product produced during the commercial preparation of α-naphthylamine), like PBNA, is metabolized in laboratory dogs to BNA.

In a study by DuPont, 2-nitronaphthalene was fed (100 mg/kg and 50 mg/kg) to a female Beagle dog and β-naphthylamine was found in the urine. In another study (conducted by Allied Chemical), four female dogs were fed 100 mg of 2-nitronaphthalene daily for 8 months. After 10.5 years, bladder papillomas were observed in various stages of malignancy in the 3 dogs for which autopsy results were available. Allied concluded from this study that 2-nitronaphthalene is an active carcinogen in the female dog. In addition, 2-nitronaphthalene has been shown to be metabolized in monkeys to BNA (JNCI, 50:989-95, 1973). However, there are no reports concerning the metabolic fate of 2-nitronaphthalene in man.

RECOMMENDATIONS

The fact that certain substances, as illustrated by PBNA and 2-nitronaphthalene, can be metabolized to known carcinogens, lends a new perspective to controlling workplace hazards. NIOSH therefore recommends that:

> Industrial hygiene practices should be followed to minimize exposure to phenyl-β-naphthylamine in the workplace (attached).

- Although there are a number of antioxidants which may be substituted for phenyl-β-naphthylamine, alternatives should be fully evaluated with regard to possible human effects.

- More consideration should be given to the assessment of metabolic pathways of chemical agents found in the workplace.

- Materials which can be metabolized by the human body to known carcinogens should be handled in the same manner as carcinogens.

The National Institute for Occupational Safety and Health is making recommendations to the Occupational Safety and Health Administration (OSHA) for regulatory action.

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Director

Enclosure

INDUSTRIAL HYGIENE PRACTICES TO MINIMIZE EXPOSURE TO PHENYL-β-NAPHTHYLAMINE

The recent confirmation of β-naphthylamine as a metabolic by-product, as well as a contaminant of phenyl-β-naphthylamine (PBNA) has indicated the need for minimizing exposure to PBNA. The following are suggested good industrial hygiene practices.

A. Regulated Area. Regulated areas should be established where PBNA is manufactured, processed, used, repackaged, released, handled or stored.

1. Access. Access should be restricted to employees who have been properly informed of the potential hazard of PBNA exposure and proper control methods.

2. Engineering Controls. The most effective control of any potentially toxic substance is control at the source of generation. Effective engineering measures include the use of walk-in hoods or specific local exhaust ventilation with suitable collectors.

3. Respirators. Personal respiratory protective devices should only be used as an interim measure while engineering controls are being installed, for non-routine use and during emergencies. Considering the carcinogenic potential and the lack of a standard, the appropriate personal respiratory protective measure is the use of a positive pressure supplied air respirator or a positive pressure self-contained breathing apparatus.

4. Protective Clothing. Protective full body clothing should be provided and its use required for employees entering the regulated area. Upon exiting from the regulated area, the protective clothing should be left at the point of exit. With the last exit of the day, the protective clothing should be placed in a suitably marked and closed container for disposal or laundering. (Laundry personnel should be made aware of the potential hazard from handling contaminated clothing.)

5. Personal Cleanliness. Employees should be required to wash all exposed areas of the body upon exiting from the regulated area.

6. Empty Containers. Empty PBNA containers should be placed in impervious bags to reduce possible contamination. These containers should be disposed of in a safe manner.

B. Medical Monitoring. All employees with a potential exposure to PBNA should be placed under a medical monitoring program including history and medical examinations to detect the presence of bladder cancers and specific urine analysis for β-naphthylamine.

C. Substitution. The substitution of another antioxidant for PBNA is a possible control measure. However, alternatives to PBNA should be fully evaluated with regard to possible human effects.

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