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Survey for N-nitroso Compounds

at

Procter & Gamble

Quincy, MA

March 19, 1980

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New England Institute for Life Sciences
Waltham, MA

and

National Institute for Occupational Safety and Health
Cincinnati, OH

Place Visited	Procter & Gamble, Quincy, MA
Date of Visit	March 19, 1980
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Purpose of Visit	To determine whether N-nitroso compounds are present or formed in the surfactant and detergent industry.

Introduction

N-nitroso compounds (nitrosamines) have the general formula R_1R_2N-NO, with R_1 and R_2 being virtually any organic group. These compounds are usually formed by the reaction of a secondary amine with nitrite in an acid solution (1, 2), however these are not the only conditions that can give rise to these compounds. It has been demonstrated that N-nitroso compounds can be produced in: organic solvents (3), alkaline solutions (4), gas phase reactions (5), and on surface via airborne oxides of nitrogen (6, 7). Tertiary amines have also been shown to form N-nitroso compounds (8). The nitrosyl radical (-NO) can be derived from oxides of nitrogen (X-NO, NO_2, N_2O_3 or N_2O_4) (4, 5, 6, 7), organic and inorganic nitrite or via trans-nitrosation by other N-nitroso compounds (9). It has also been shown that these reactions can be increased by catalysts such as formaldehyde or chloral (10), or metal ions (11) and that they can be inhibited by α-tocopherol (12), ascorbate (13), and sulfamic acid (14). In short, these compounds can be produced in almost any situation where the precursors co-exist.

Interest in the possible human health hazard that N-nitroso compounds may pose began following the observation in animal studies of the toxic and carcinogenic effects of N-nitrosodimethylamine (NDMA) (15). The toxic effect of NDMA on humans was first reported by Freud in 1937 (16) who described its hepatotoxic effects on two chemists that had been accidentally poisoned by this compound. Since these

first findings, N-nitroso compounds have been studied extensively in experiments with laboratory animals. More than 100 of the 130 different compounds tested have been shown to be carcinogenic (15, 17, 18, 19). N-nitrosodiethylamine (NDEA), for example, has been tested in the rat, African white-tailed rat, mouse, S.G. hamster, Chinese hamster, European hamster, guinea pig, rabbit, dog, pig, trout, grass parakeet and monkey, and has been shown to be carcinogenic in all these species.

The site where the tumor developed depended upon the chemical structure of the N-nitroso compound, the animal being tested and on the route of administration. N-nitroso compounds have been shown to affect the bladder, bronchi, central nervous system, earduct, esophagus, eyelid, duodenum, forestomach, glandular stomach, hematopoietic system, intestine, jaw, kidney, larynx, lung, nasal cavity, oral cavity, ovary, liver, mammary glands, pancreas, pelvis, peripheral nervous system, pharynx, respiratory tract, skin, testis, tongue, trachea, uterus and vagina (18).

Three N-nitrosamines that were tested in dose response studies with rats were shown to be extraordinarily potent carcinogens. The apparent 'no effect level' at which no statistical difference between the test animals and the controls could be observed, was found to correspond to dietary levels of 1000 µg/kg (1 ppm) of N-nitrosodimethylamine (20), 1000 µg/kg (1 ppm) of N-nitrosodiethylamine (21), and 5000 µg/kg (5 ppm) of N-nitrosopyrrolidine (22). Thus, in a rat population of under 100 animals, between 1 and 5 ppm of these

nitrosamines in the diet were marginally carcinogenic.

The comparative *in vitro* metabolism of N-nitrosodimethylamine is similar in both the human and rat liver (23). Furthermore, the rate of metabolism in human liver slices is comparable to that in the rat liver, with the levels of nucleic acid methylation being similar to the two species (24). In acute toxicity experiments with high doses, nitrosamines generally produce centrilobular necrosis in most animal species.

While many of these compounds have been demonstrated to be potent animal carcinogens, their carcinogenic risk to man (the probability that defined exposure to these chemicals will lead to cancer) has not yet been determined. In order to assess this risk it is first necessary to locate sufficient populations of exposed people.

Until as recently as 1975 the primary interest in human exposure to these carcinogenic compounds centered around their occurrence in nitrite preserved foods, cheese products, fish and fish meal, biological samples, tobacco, alcoholic beverages and *in vivo* formation from precursor chemicals. With the finding of NDMA in the atmospheres near manufacturing facilities producing and/or using dimethylamine (25, 26, 27) the emphasis on human exposure to these compounds began to shift to the workplace where, it has been speculated, human exposure to these compounds may be the highest (25).

Further discoveries of N-nitroso compounds in cosmetics (28), tobacco smoke (29), indoor atmosphere under conditions of excessive tobacco smoking (30), in synthetic cutting fluids (31), and in some

widely used herbicides (32), have further shifted the emphasis of the environmental search for human exposure to these compounds. It is now apparent that in any situation where the precursors of these compounds (amines and nitrosating agents) exist together, there is a high likli-hood of finding N-nitroso compounds.

Many secondary amines such as dimethylamine, diethylamine and morpholine are produced in large quantities for both industrial and consumer use. Products manufactured from these amines are used in agricultural chemicals, detergents, rust inhibitors, rubber additives, solvents, drugs, plastics, leather tanning, textiles, cosmetics and in synthetic cutting and grinding fluids (33). Given the widespread use of secondary amines and the ever present nitrogen oxides of an industrial society, the likelihood of N-nitrosamines being formed in some products or in an industrial situation where these compounds may occur together, is high.

Until this study the human population groups that were identified as being potentially exposed to large amounts of carcinogenic N-nitroso compounds included; chemical workers at a factory making unsymmetrical dimethylhydrazine from N-nitrosodimethylamine (26, 34), agricultural workers handling pesticides contaminated with nitrosamines (32), machinists using synthetic cutting and grinding fluids contaminated with N-nitrosodiethanolamine (31), and persons using facial cosmetics contaminated with N-nitrosodiethanolamine (28). During this present study two other groups: rubber workers exposed to N-nitrosomorpholine (35) and leather tanners exposed to

N-nitrosodimethylamine in tannery air (36) have also been discovered.

The knowledge that humans may be exposed to N-nitroso compounds is a recent development which may have important implications in carcinogenesis. If N-nitroso compounds are a cause of cancer in man, then minimizing exposure to these compounds could be a significant milestone in cancer prevention. But direct evidence for the carcinogenicity of N-nitroso compounds in man is lacking. There is, however, a substantial amount of circumstantial evidence which makes it unlikely that man alone will be resistant to their carcinogenic assault. Recent advances in epidemiology, plus improved technology in the analytical chemistry of N-nitroso compounds, coupled with a better understanding of the formation chemistry of N-nitroso compounds, makes it possible to begin "the quest" for evidence which may answer the question of whether or not these compounds are carcinogenic in man.

Until epidemiological assessments can be made it must be assumed, on the basis of many animal studies, that man will not be uniquely resistant to the carcinogenic action of nitrosamines. Indeed if human populations are found to have excessive exposure to these compounds, prompt action should be taken to eliminate or reduce their exposure. Since cancer produced from carcinogenic compounds is a delayed toxic effect, and since animal studies show dose related responses to these agents, it would be prudent to assume (until evidence can be obtained) that any exposure to the carcinogenic N-nitrosamines constitutes a risk. This study by the National Institute for Occupational Safety and Health (NIOSH) is the first attempt to determine workers' exposure to N-nitroso compounds in a variety of industrial facilities. It assesses not only the extent of worker exposure to these agents, but also how they are exposed and how best to eliminate or reduce their risk.

Soap, Detergent and Surfactant Industry

Interest in surveying this industry for the presence of N-nitroso compounds and the possibility that workers may be exposed to these agents is due to its production of amine-derived cationic surface active agents (37). This industry also produces anionic detergents and soap. The production of anionic detergents and soaps from arylalkyl-sulfonates, fats, waxes and oils of plants and animals does not involve the use of amines and, therefore, seems an unlikely source for N-nitroso compounds. However, in producing cationic surface active agents, primary, secondary and tertiary amines are used. These amines could, if a suitable N-nitrosating agent were present, give rise to N-nitroso compounds. Some of the sources for these nitrosating agents include airborne oxides of nitrogen, drying processes where combustion gas is passed over the product (drying towers) and gas driven lift trucks. As evidence that N-nitroso compounds may be associated with the production of cationic surfactants, 0.15 $\mu g/m^3$ of NDMA was found in an air sample adjacent to a detergent manufacturing facility in Jersey City, New Jersey, in August of 1978. This facility was manufacturing cationic surfactants at the time that Thermo Electron Corporation, under contract to EPA, made this finding. With this finding and the known use of nitrosamine precursors, a more extensive industry-wide survey of the soap and detergent industry for possible worker exposure to N-nitroso compounds seemed warranted.

Many of these cationic surfactants are secondary, tertiary or quaternary amines which could, in the presence of a suitable N-nitrosating agent, give rise to N-nitroso compounds.

Plant Description

This plant employees 250 workers in the production area and 50 in management and operates 3 shifts, 5 days/week, producing synthetic laundry detergents and soaps. It has been in operation since the 1940's and does not produce cationic surfactants. The raw materials used at this facility consist of linear alkyl benzenes, fatty alcohols, oleum, sulfuric acid, sodium hydroxide, a variety of dry additives and perfumes. The manufacturing process consists of sulfating the alkyl benzene or fatty alcohols followed by neutralization with sodium hydroxide. Dyes and additives are added and the product dried via hot air in a tower. Perfumes, admixes, softening ingredients, etc., are then added to the dry product prior to packaging it. The product is then stored in a warehouse for later distribution to retail outlets. The only cationics used at this facility are softening agents which are added to some of the products. The softening agent used at this plant is Di-tallow dimethyl ammonium chloride.

The drying tower is heated by direct oil heat. During our initial plant tour we observed several propane driven fork lift trucks which could be a source for airborne oxides of nitrogen.

Plant Survey Protocol

In order to assess the potential worker exposure to N-nitroso compounds, environmental samples consisting of air and bulk samples are collected and analyzed using a mobile laboratory equipped for N-nitroso compound analysis (43). The on-site survey usually consists of examining the facility for areas or processes where these compounds could be present followed by sampling those suspected areas. In most instances, both air and bulk samples are collected for analysis.. The air samples are usually area samples, however, specific

specific process air samples can be collected to determine if a point source could be responsible for the presence of any discovered N-nitroso compounds.

Sampling

Air Sampling

At this plant on March 19, 1980, five area air samples were collected by NEILS and analyzed for N-nitroso compounds. Also three shorter samples using a high volume air pump were collected. The volume of air sampled varied at each site. For the area samples between 230 and 358 liters of air were sampled. Each of the high volume samples collected 100 liters. ThermoSorb/N air samplers were used in each case. ThermoSorb/N air samplers have been tested by Rounbehler et al. (6,7) and were found to quantitatively retain N-nitrosamines without the formation of artifacts even in the presence of amines and nitrogen oxides, typical N-nitrosamine precursors. Adsorbed nitrosamines can be quantitatively desorbed from the ThermoSorb/N cartridges by backflushing with 1.5 - 2.0 ml of a 25% solution of methanol in methylene chloride. This desorbing solution is then examined for the presence of N-nitroso compounds.

Analysis by GC-TEA

The GC-TEA conditions used for the detection of volatile nitrosamines are those described by Fine and Rounbehler (40). A 14' x 1/8" stainless steel column packed with 10% Carbowax 20M containing 0.5% KOH on Chromosorb HP (80-100 mesh) was operated at 150°C with argon gas as the carrier at a flow rate of 15 ml/min. A TEA, which is a nitrosamine-specific detector (41) was used with a specially designed dry trap instead of the usual cold trap.

Analysis by HPLC-TEA

HPLC-TEA was constructed by sequentially connecting a high pressure pump (Altex Model 110), an injector (Waters), a Lichrosorb Si60 column (E. Merck Labs, 4mm x 39cm), and a TEA^{TM} (Thermo Electron). The operation of the HPLC-TEA has been described by Fine et al (42). A 2 ml/min flow rate was used with a solvent system consisting of 4% acetone and 96% isooctane.

Discussion

No N-nitroso compounds were found in this plant's atmosphere on the day that it was sampled. These findings were, however, not unexpected since this facility did not use amines in its processes.

Results

Procter & Gamble - Quincy, MA
March 19, 1980

Sample No.	Collection Method	Sample Location	N-nitroso Compound Detected
02661	ThermoSorb/N	MSG Table Area	N.D.
02662	ThermoSorb/N	5th Floor Finished Products	N.D.
02663	ThermoSorb/N	4th Floor Finished Products	N.D.
02664	ThermoSorb/N	3rd Floor Packing Room Line 9	N.D.
02665	ThermoSorb/N	Soap Process Near Neutralizer	N.D.
00991	ThermoSorb/N	2nd Floor Soap Processing	N.D.
00990	ThermoSorb/N	Glueing Operation on Packing Line	N.D.
00989	ThermoSorb/N	Warehouse Unit Load Former	N.D.

N.D. - None Detected, detection limit 0.03 $\mu g/m^3$.

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