

Exposure Assessment to Preformed Environmental N-Nitroso Compounds from the Point of View of Our Own Studies

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Key Words. Nitrosamines · Work place · Tanning · Rubber · Tires · Rocket fuel · Cosmetics · Cutting fluids · Herbicides · Drugs · Beer

Abstract. The largest human exposure to N-nitrosamines is in the industrial section. Leather tanners are exposed to N-nitrosodimethylamine at levels up to $47 \mu\text{g}/\text{m}^3$, corresponding to $440 \mu\text{g}/\text{person}/\text{day}$. Workers in the curing area of tire factories are exposed to N-nitrosomorpholine at levels up to $27 \mu\text{g}/\text{m}^3$, corresponding to an intake of $250 \mu\text{g}/\text{person}/\text{day}$. These industrial exposures are considerably greater than exposure via food-stuffs, beer, cosmetics, cutting fluids and herbicides.

Introduction

N-nitroso compounds form readily from a variety of amine-type compounds and nitrosating agents. The amines can be primary, secondary or tertiary. The nitrosating species can be derived from nitrite salts or nitrous acid, oxides of nitrogen (NO , NO_2 , N_2O_3 , N_2O_4), nitro compounds ($\text{O}-\text{NO}_2$, $\text{N}-\text{NO}_2$, $\text{C}-\text{NO}$) or by transnitrosation from nitroso compounds ($\text{O}-\text{NO}$, $\text{N}-\text{NO}$ and $\text{C}-\text{NO}$). Depending on the reactants and the presence of catalysts, N-nitroso compound formation can occur at acidic, neutral or alkaline pH, or in organic media. Because N-nitroso compounds can be formed so readily from such a variety of widely distributed precursors, it is not surprising to find that low levels of N-nitroso compounds are ubiquitous in the environment. This discussion will deal with human exposure to N-nitrosamines which we have found from our own studies.

Workplace Exposure to Airborne N-Nitrosamines

The human beings who receive the largest daily intake of N-nitrosamines are factory workers in a

posure to N-nitrosodimethylamine (NDMA) is to leather tanners [Rounbehler *et al.*, 1979], particularly those who work in the wet tanning area. NDMA has been found to be present in all of the 5 tanneries which have been visited [Fine *et al.*, 1979], at levels varying from $2-3 \mu\text{g}/\text{m}^3$ to as high as $47 \mu\text{g}/\text{m}^3$. The daily human exposure from this source can be as high as $440 \mu\text{g}$ (table I). In addition, N-nitrosomorpholine (NMOR) at a level of $2.0 \mu\text{g}/\text{m}^3$ has been shown to be present in the finishing area of one of the tanneries where the surface of the hides are chemically doped. To our knowledge, no epidemiological studies have been reported on leather tanners. The US National Institute for Occupational Safety and Health is planning a nitrosamine-leather tanner epidemiology study.

The curing and extrusion areas of rubber tire factories have been shown to contain NMOR, at levels from 0.5 to $27 \mu\text{g}/\text{m}^3$ [Fajen *et al.*, 1979]. The daily human exposure produced by these levels is between 50 and $250 \mu\text{g}$. NMOR probably arises as a trace contaminant in bismorpholinecarbamylsulfenamide, which is used as an accelerator. It is of interest to note that several recent studies agree that lung and gastrointestinal cancers occur at increased risk among workers in several of these same areas [Monson and Fine, 1978;

Table 1. Industrial exposure to airborne N-nitrosamines

	Daily ¹ exposure, $\mu\text{g}/\text{day}$				
	NDMA		NMOR		NDPhA
	high	average	high	average	high
Leather tanning	440	20-180	20		
Tire curing			250	50-130	
Tire chemical factory	5				430
Iron foundry	10				
Vinyl fabric warehouse	4	2			
Rocket fuel production	260	10-50			

¹ It is assumed that an average worker weighs 70 kg (1.85 m² body surface area) and breathes 20 liters/min for an 8-hour work day.

et al., 1976; *McMichael et al.*, 1976; *Andjelkovich et al.*, 1977). However, at this point further speculation on the possible involvement of N-nitroso compounds in the etiology of rubber worker cancer is premature. We know of two US epidemiology studies which are planning to investigate the nitrosamine-rubber worker link.

NDMA was found to be present as an air pollutant at several rubber factories, at lower levels (0.05–0.5 $\mu\text{g}/\text{m}^3$). N-nitrosodiphenylamine (NDPhA) was found at the 0.2–47 $\mu\text{g}/\text{m}^3$ level in a chemical factory where NDPhA was being manufactured for use in tires. The whole area was contaminated with NDPhA, with a mud scraping from the floor containing 15,000 $\mu\text{g}/\text{g}$ NDPhA. Daily exposure to NDPhA by workers in this factory was in the 5–430 μg range.

NDMA was reported to be present on the site of a rocket fuel factory where unsymmetrical dimethylhydrazine was being manufactured from NDMA [*Fine et al.*, 1976a, b]. On the site of the factory, NDMA air levels varied between 2 and 36 $\mu\text{g}/\text{m}^3$. The average daily NDMA intake of workers was between 10 and 50 μg .

Recently, NDMA and NDEA have been detected at the 1–2 $\mu\text{g}/\text{m}^3$ levels inside an iron foundry [*Fine and Rounbehler*, unpublished data, 1979]. Further work in this industry is continuing.

Dermal Exposure

N-Nitrosodiethanolamine (NDEIA) was found by *Fan et al.* [1977a] to be a contaminant in the concen-

trates used for synthetic cutting fluids. Although the fresh fluids contained NDEIA at levels as high as 3%, NDEIA could not be detected inside large machine shops which were using many automatic machine tools containing a contaminated cutting fluid [*Fine and Fan*, unpublished data, 1978]. It is difficult to estimate absorption of NDEIA through the skin of a worker whose hands are in contact with the fluids. Many US manufacturers now advertise 'nitrosamine-free' cutting fluids.

NDEIA was also shown to be a contaminant in 5 out of 6 facial cosmetics at concentrations of between 40 and 48,000 $\mu\text{g}/\text{kg}$ [*Fan et al.*, 1977b]. Hand lotions and hair shampoos were also shown to be contaminated, at concentrations of between 22 and 260 $\mu\text{g}/\text{kg}$. A recent report by *Edwards et al.* [1979] showed that NDEIA was present in the urine of a person wearing an NDEIA contaminated cosmetic which had been purchased over the counter. Approximately 1.7% of the NDEIA which was applied to the skin for 8 h showed up as NDEIA in the urine over a 21-hour period. Recent studies by the FDA [*Weninger*, 1979] report that many US cosmetics are to this day contaminated with appreciable levels of NDEIA.

Commercial formulations of widely used amine salt and dinitroaniline herbicides were reported to be contaminated with N-nitrosamines [*Fine et al.*, 1976a, *Ross et al.*, 1977]. Since these reports, the manufacturers have been successful in reducing the levels of N-nitrosamines in their products. Thus, whereas we found NDMA at the 640 $\mu\text{g}/\text{ml}$ level in a formulation of the dimethylamine salt of 2,3,6-trichlorobenzoic acid, within 12 months after the finding was made public the nitrosamine level had been reduced to less than 2 $\mu\text{g}/\text{ml}$ [*Fine*, 1980; *Cohen and Bachman*, 1978]. Similarly, the N-nitrosodipropylamine contamination in formulations of the herbicide Trifluralin were reduced from 195 to less than 1 $\mu\text{g}/\text{ml}$.

Herbicides such as the dinitroanilines are generally applied by soil incorporation. *Ross et al.* [1977] have conducted measurements in a tomato field during application of Trifluralin; they were unable to detect N-nitrosodipropylamine either in the soil, in the runoff water, or in the air above the field. However, workers who operate the agricultural equipment have presented testimony at an Environmental Protection Agency hearing that their hands and clothing are often soaked in the herbicide. These agricultural workers may have been subject to significant exposures to N-nitrosodipropylamine.

Ingestion

Ingestion is the most widely studied route of human exposure to N-nitrosamines and studies are well documented for a wide variety of foodstuffs [IARC, 1978]. Other articles in this issue cover this aspect more fully.

Because many drugs contain the amine-type structure, we examined 73 prescription and over-the-counter drugs for N-nitroso compounds [Krull *et al.*, 1979]. Only three formulations; phenylzine sulfate (0.08 $\mu\text{g/g}$), imipramine HCl (0.07 $\mu\text{g/g}$) and nitrofurantoin (0.04 $\mu\text{g/g}$) were found to contain any impurities which could be N-nitroso compounds. The structural identity of these impurities have not yet been determined. It would seem, therefore, that apart from aminopyrine [Eisenbrand *et al.*, 1978, 1979], drugs may not constitute a widespread source of human exposure to preformed N-nitrosamines.

We have confirmed Spiegelhalder *et al.*'s [1979] finding that German beers contain NDMA. We find similar results in beer from Australia, France, Greece, Holland, Ireland, Japan, Mexico, Philippines, United Kingdom and the US (average 3.0 $\mu\text{g/l}$). We have also screened other alcoholic and nonalcoholic beverages for N-nitrosamines, with a sensitivity of 0.2 $\mu\text{g/l}$. We found NDMA in 6 out of 7 Scotch whiskies, at the 0.3 to 2.0 $\mu\text{g/l}$ level [Goff and Fine, 1980]. However, volatile N-nitrosamines were not detected in 22 US and imported wines, 4 liqueurs, 3 gins, 4 brandies, 3 vodkas, 3 rums and 5 US whiskies.

Conclusions

Knowledge about man's exposure to preformed N-nitrosamines is expanding rapidly, with much of the data presented here only becoming available within the past 12 months. It would be unwise to assume that we now know everything about man's exposure to preformed N-nitrosamines. In the industrial area, we suspect that several types of industries may have N-nitrosamine exposures as large as that of tire workers and leather tanners, and further research is underway.

Acknowledgments

Much of the work described here was supported by the National Science Foundation under Grant No. ENV7520802, the National Institute of Occupational Safety and Health under Contract 210-77-

0100 and the Environmental Protection Agency under Contracts Nos. 68-02-2766, 68-02-2363, 68-02-2312 and 68-03-2400.

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