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NITRITE AND NITROSAMINE UPDATE

Nitrosamine research has expanded rapidly in the past two years. Nitrosamines have been found in non-food substances, in the air, and in water; interest has shifted to *in vivo* formation; and more sensitive and selective analytical methods have been developed. I can't even begin to give you a proper up-date in the short time allotted to me so I will just touch on a few areas that I think will be of most interest.

Analytical

Analytically, smaller and smaller concentrations of nitrosamines are being determined; ng/kg, or ppt, of nitrosamines are reported in food products. A new detector, the Thermal Energy Analyzer (TEA) (Fig. 1), is being used extensively. Briefly, the nitrosamine emerging from the gas-chromatograph (gc) is pyrolyzed in the oven and the NO released is reacted with ozone. Excited NO₂ is produced, which, on decaying to the ground state, produces chemiluminescence that is detected by the photomultiplier tube.

The instrument is very sensitive and more selective than other detectors. The quantifiable concentration of nitrosamine has been reduced below the range of confirmation by mass spectrometry (ms), which poses a problem. Doerr and Fiddler (1977) have developed a procedure that tentatively confirms the presence of nitrosamines (Fig. 2). If the gc-TEA indicates the presence of a nitrosamine, several μ l of sample in a melting point capillary tube are exposed to UV at 366 nm for two hours and run through the gc-TEA again. Nitrosamine peaks disappear. This is a good "presumptive" test and has reduced the number of samples requiring confirmation.

Nitrosamines in Foods

In the foods area current surveys in several countries continue to find nitrosamines in meat products, cheese, fish and prepared dinners, but the levels are lower than previously found. Gough (1977) in England had run a survey on a variety of foods using gc-ms and found NDMA⁺ and NPYR at 1 ppb level in some products only, but when similar items were examined with gc-TEA many were found to contain < 1 ppb. In another series Gough et al. (1978) analyzed 50 cooked bacon samples and found 1-20 ppb NPYR in all of them. NPIP, which was not reported consistently previously, was now found in the 50

samples at 0.08-0.25 ppb, or 80-250 ppt. Some other meat products contained several nitrosamines, each at the 0.1-1.0 ppb level. They also analyzed some meals and estimated the total weekly intake of volatile nitrosamines from English food (Table 1). The likely intake of dialkyl and heterocyclic nitrosamines is 1 μ g and 3 μ g/week, respectively. Stephany et al. (1976) examined 36 Dutch meat products and found low levels of nitrosamines. None of these samples showed more than 5 ppb of NDMA, NDEA or NDBA, and 95% of the samples contained less than 10 ppb NPYR or 5 ppb NPIP. Fifty percent of the samples contained less than 0.4 ppb of NDMA, NDEA, NPYR, or NPIP.

In order to measure such low levels of nitrosamines, both Gough's and Stephany's groups used larger samples of meat than are commonly analyzed in the U.S. (250 to 500 gm vs. 25 gm). The larger samples, however, contribute more interfering compounds that have to be removed. If the presence of such low concentrations of nitrosamines becomes a critical regulatory factor, particularly at the international level, the differences in sample size will have to be taken into consideration.

Nitrosamines in Non-Food Sources

In the non-food area, NDMA was found in six formulations of herbicides in concentrations ranging from 0.3 to 640 ppm (Ross et al., 1977). The herbicides were formulated as dimethylamine salts; the dimethylamine probably reacted with the sodium nitrite that was used as a rust-inhibitor in the metal containers. A seventh herbicide was made with nitric acid followed by a reaction with dipropylamine; 154 ppm NDPA was found. Cutting oils were also found to contain nitrosamines. Almost all metal cutting oils are synthetic, containing up to 45% triethanolamine and 18% NaNO₂. Eight brands were analyzed (Fan et al., 1977b) and found to contain 0.02-2.99%

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THERMAL ENERGY ANALYZER

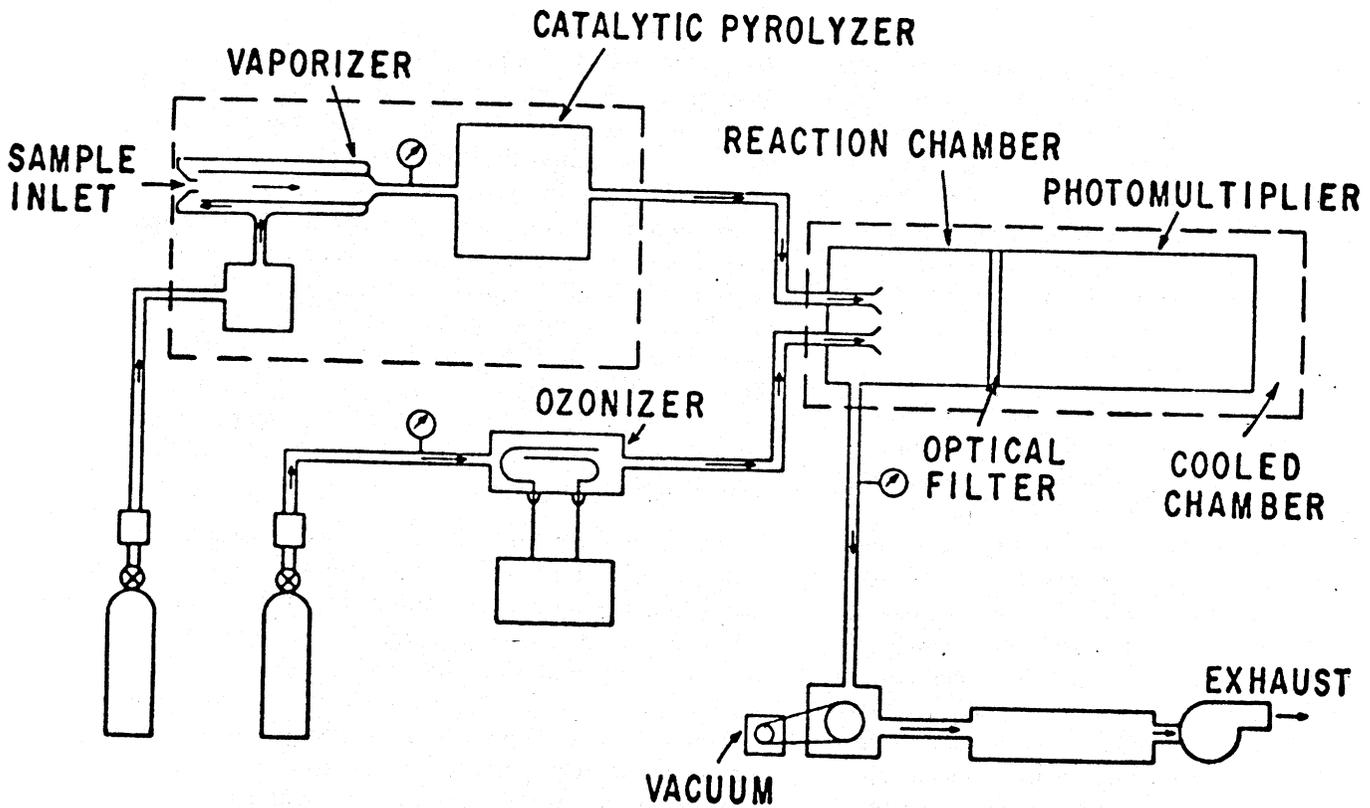


FIGURE 1

Schematic of Thermal Energy Analyzer.

TABLE 1

ESTIMATED WEEKLY INTAKE OF VOLATILE NITROSAMINES FROM UK FOOD

Food	Consumption (kg per week per person)	Dialkyl nitrosamines		Heterocyclic nitrosamines	
		Average Concentration (μg per kg)	Intake (μg per week)	Average Concentration (μg per kg)	Intake (μg per week)
Cured meats	0.34	1.0	0.34	8	2.7
Fish	0.14	0.2	0.03	—	—
Cheese	0.10	0.4	0.04	—	—
All other foods	9.62	0.06	0.58	—	—
Totals	10.20		0.99		2.7

(Gough et al., 1978)

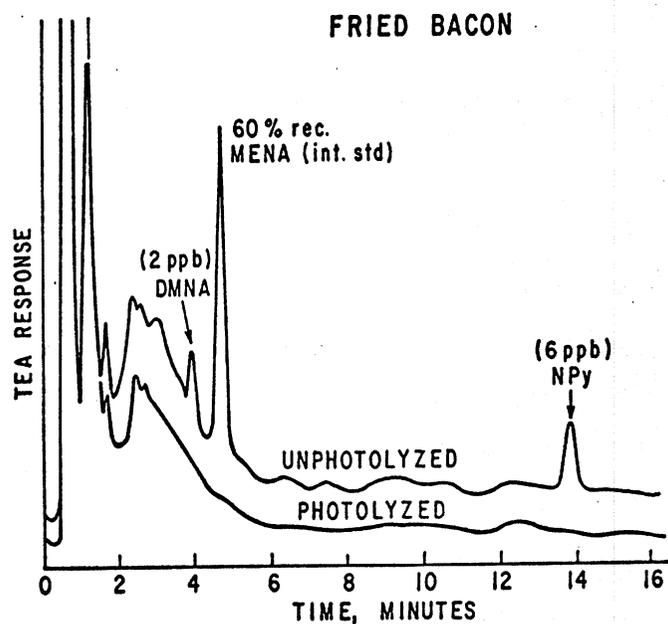


FIGURE 2

Effect of Ultraviolet Photolysis (at 366 nm) on Nitrosamines in Fried Bacon Extract.

NDELA Triethanolamine is also used as an emulsifier in skin preparations such as cosmetics, lotions and shampoos. Fan et al. (1977a) reported < 10 to 140 ppb NDELA in seven cosmetic preparations and < 10 to 280 ppb in 10 shampoos. Use of cosmetics may result in exposure to 50-100 ppb NDELA daily. The source of NDELA is not known, but it is possible that the triethanolamine degrades to diethanolamine which can react with nitrogen oxides in the air. Nitrosamines have been found in the air, particularly at point sources where either the nitroso compound or the precursor amine exists in high concentrations. At Belle, W. Va., up to 0.51 ppb NDMA was found near a plant making dimethylamine, and 0.96 ppb NDMA was identified in Baltimore where unsymmetrical dimethylhydrazine was being produced (Fine et al., 1975). Breitschneider and Matz (1975) also found NDMA associated with manufacturing activities.

Formation of nitrosamines in the atmosphere is possible if free amines react with nitrogen oxides particularly where a high SO_2 concentration produces acid conditions, but UV photodecomposition appears to counterbalance the formation.

A number of peaks detected by TEA in Mississippi water have been reported as "unidentified" nitrosamines (Fine et al., 1975). One peak, originally identified as nitrosoatrazine was subsequently found to be ethylene glycol dinitrate. In our laboratory we found

NDMA and NDEA in deionized water at a concentration of up to 0.2 ppb (Fiddler et al., 1977).

In Vivo Formation

Evidence for potential nitrosamine formation *in vivo* is beginning to accumulate. Precursors are present in food, water and saliva. Nitrite is a normal constituent of saliva in concentrations on the order of 10 ppm and is produced through reduction of nitrate by oral bacteria. When vegetables, high in nitrate are ingested, the nitrite concentration of the saliva can increase to hundreds of ppm in a few hours (Fig. 2). Purslane, a leafy salad green, induced high salivary nitrite for several hours (Stephany and Schuller, 1977), as did cucumber and lettuce (Stephany and Schuller, 1977) and celery juice (Tannenbaum, 1976). High nitrate concentration in the drinking water has been postulated to induce stomach cancer in some areas of Colombia, South America (Cuello et al., 1976). Nitrate is reduced in the mouth, esophagus or stomach (Tannenbaum, 1976), and the resulting nitrite reacts with amines in the gastric tract. In Iran, however, high nitrate in the water could not be related to the high incidence of esophageal cancer in which nitrosamines were thought to be a causal factor (Bogovski, 1976).

Dimethylamine, pyrrolidine and other amines occur in the urine. Nitrate is also a normal urinary constituent. In the presence of nitrate-reducing bacteria nitrosamine formation is possible. The urine of women with urinary tract infections contained NDMA (Radomski and Hearn, 1976) as did that of patients with bacterial cystitis, bladder cancer and bilharzial infections of the bladder (Hicks et al., 1977).

Human Studies

Preliminary experiments on nitrosamine formation in the human stomach have been reported. Walters (1976) fed 14 volunteers milk, egg and luncheon meat and analyzed the stomach contents at various times. NPIP (0.3-0.5 ppb) was found in four subjects within 60 minutes; three were smokers, one was not. In another study Fine et al. (1977) fed a volunteer bacon, spinach, tomato, bread and beer. Although NPYR was present in the meal none was found in the volunteer's blood. NDMA was detected in the blood at a lower concentration than in the food.

We have surveyed the fasting gastric contents of 35 patients, some before and after pentagastrin or histamine stimulation (Lakritz et al., 1977) (Table 2). Of 57 samples, seven contained confirmable levels

TABLE 2
NITROSAMINES IN HUMAN GASTRIC CONTENTS

Patient	Nitrosamine		NO ₂	NO ₃	pH	Diagnosis
	Compound	μg/kg	mg/kg			
1	NDEA	30	69		1.6	Duodenal ulcer
	NDEA*	26	76		1.5	
2	NDEA	5			2.2	Marginal ulcer
3	NDEA	23			2.9	Marginal ulcer and cirrhosis of liver
4	NPYR*	6			6.4-7.5	Atrophic gastritis
5	NDMA	2	0	26	2.9	Not known
6	NDMA*	2			1.9	Gastritis, duodenitis

*These samples were obtained following gastric secretion stimulation with histamine or tetagastrin. (Lakritz et al., 1977)

of nitrosamines. Several samples contained "apparent" nitrosamines at levels too low to confirm.

More human studies with normal diets are needed to evaluate the possibility of *in vivo* nitrosation.

Animal Experiments

Numerous animal studies show that either *in vivo* formation from large concentrations of precursors or the ingestion of the nitrosamines themselves induce tumor formation. These studies have been criticized for the high concentrations used because they may affect normal metabolic pathways or because they may override the DNA repair mechanism that is currently under study (Magee, 1976). Although the con-

cept of a threshold, or no response, dose for carcinogens has been discounted (Kennedy, 1978), several recent studies show that nitrosamines at some concentration in the diet induced no significant increase in tumors in rats. Olsen and Mayer (1976) fed two generations of rats a semi-synthetic diet containing 45% canned, cured meat as sole protein source. Even with the meat cured with 4000 ppm nitrite and containing NDMA no significant increase in tumors was found (Table 3). A 3 year Canadian study, just completed, involved feeding rats commercial bacon as 25% of their diet. The bacon was cured with 150 ppm nitrite and had 39 ppb nitrosamines. No significant increase in tumors occurred. Preussmann et al. (1976) incorporated 10, 3, 1.0 or 0.3 mg NPYR/kg body weight in the daily drinking water of groups of rats (Table 4). Tumor formation was found at the three highest levels, but at 0.3 mg/kg the number of tumors was

TABLE 3

TUMOR FORMATION IN RAT-FEEDING* STUDY

Group	Nitrite added mg/kg	Rats with tumors	
		Benign	Malignant
1	0	62	24
2	0	124	44
3	0	68	22
4	200	70	22
5	1000	67	21
6	4000**	74	30

*Diet contained 45% cured meat as protein source
**Only treatment in which NDMA was found (Olsen and Mayer, 1976)

TABLE 4

Daily Dose mg/kg	No. rats	NITROSOPYRROLIDINE AND TUMOR FORMATION With tumors		Time of Death, days
		Malignant	Benign	
0	61	6	5	(587)
0.3	60	12	8	664
1.0	62	20	9	685
3.0	38	32	3	533
10.0	24	11	6	444

(Preussmann et al., 1976)

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not significantly greater than in the controls. The "no effect" dose corresponds to 5 ppm in the diet. There was also an increase in the latency period for tumor induction with decreasing doses of NPYR, so it is possible that at low levels of nitrosamine the latency period could extend beyond the life span of the animal and no tumor would be formed.

Mantel (1978) at the request of the American Meat Institute (AMI) analyzed Preussmann's data and calculated a "safe" level of NPYR in bacon to be 24.8 ppb for the daily consumer with a risk of less than one in a million over the lifetime.

Current Status of Nitrosamines in Cured Meat

The Expert Panel appointed by the Secretary of Agriculture in 1973 was discharged in 1977 after submitting a set of recommendations for nitrite and nitrate in cured meat products. Although many processors voluntarily stopped using nitrate and reduced the amount of nitrite in some of their products to meet the levels in the recommendations, no official action was taken until recently. The Department has ruled that bacon shall be cured with a target concentration of 120 ppm nitrite and 550 ppm ascorbate. The AMI has submitted to the Department a response on the question of nitrosamines in bacon in which they conclude that "bacon as produced today is not a health hazard, but, it is possible to reduce nitrosamine in fried bacon by lowering the amount of sodium nitrite and including sodium ascorbate or isoascorbate."

Nitrite Substitutes

Alternate procedures have been suggested to reduce or eliminate nitrite in cured meat products while still preventing the outgrowth of *Clostridium botulinum* and toxin formation. We have studied more than 200 compounds for anticlostridial activity. While many have been very effective in the test tube, they did not prevent toxin formation in meat systems. Potassium sorbate (0.1-0.2%) can be used with lower level of nitrite (40 ppm) to lengthen the lag period before packages of bacon inoculated with spores of *C. botulinum* swell (Ivey et al., 1978). A combination of 0.26% sorbate and 40 ppm nitrite was equivalent to 20 ppm nitrite (Pierson, 1978). The Department has proposed that starting in May, 1979, bacon be produced by curing with 0.26% sorbate and 40 ppm sodium nitrite. A period for comment extends until November, 1978.

Nitrosation Inhibitors

Since much of the NPYR is formed in the adipose

tissue of frying bacon the value of water-soluble ascorbate is limited. A number of studies have investigated lipophilic compounds for antinitrosation activities. Fat-soluble ascorbyl derivatives are effective in reducing nitrosamine formation. Ascorbyl palmitate, however, is insufficiently fat-soluble (Pensabene et al., 1976) or behaves inconsistently (Rubin, 1978). A series of ascorbyl acetals with increasing fat-solubility characteristics were synthesized by Rubin (1978). The C₁₆-acetal was studied in depth and 250 ppm was found to give 80-90% reduction in nitrosamine formation. A patent has been granted for use of a mixture of alkyl esters of p-benzoic acid salts with the antioxidant tert.-butylhydroxyquinone to reduce nitrosamine formation (Astill, 1977).

Laboratory studies with α -tocopherol showed the effectiveness of this fat-soluble compound in blocking nitrosation. The difficulty with this compound, however, is its limited solubility in cure solution. We have studied various Tween preparations to increase the solubility. Studies in our laboratory established the efficacy of α -tocopherol in reducing NPYR formation in fried bacon. The AMI coordinated an 8-plant study of the effects of sodium nitrite (120 and 200 ppm), sodium ascorbate (550 ppm) and α -tocopherol (0 and 500 ppm). Data in Table 5 show values obtained by TEA on fried bacon. Group A, with 200 ppm NO₂⁻ and 550 ppm Asc⁻ (which was present in all groups) had a mean of 7.58 ppb NPYR. In Group B, with 120 ppm NO₂⁻, the NPYR concentration was reduced to 4.5 ppb. α -Tocopherol, with 200 ppm NO₂⁻ yielded 2.36 ppb NPYR, and with 120 ppm NO₂⁻ lowered the NPYR level to 1.25 ppb — and 85% reduction (Mergens et al., 1977).

Risk

In all discussions of the risk of tumor formation in humans by nitrosamines the implication has been that the carcinogenic potentials of all of these compounds are the same. Reports in the literature, however, indicate some nitrosamines are strong carcinogens (NDMA, NDEA) and others are weaker carcinogens (NPIP, NSAR) based on their behavior in animals. The criteria for evaluating activity of the nitrosamines are not readily apparent. Archer and Wishnok (1977), however, have made some interesting calculations based on data from Druckery et al. (1967) and Preussmann et al. (1976). "No effect" concentrations for the three nitrosamines were determined. (Table 6). The three nitrosamines (NDMA, NDEA and NPYR) were fed to rats at the same daily dose (Table 7), and the mean carcinogenic dose (D₅₀) was determined. The reciprocals of these values in-

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TABLE 5
 α -TOCOPHEROL AND NITROSPYRROLIDINE FORMATION IN BACON

Company	A	NPYR by gc-TEA (ppb)		
		B	C	D
1	8.9	15.8	1.4	0.5
2	19.5	13.2	10.1	8.2
3	6.5	3.9	3.9	0.5
4	1.8	0.5	0.5	0.5
5	<0.5	0.5	0.5	0.5
6	7.3	4.2	0.6	0.5
7	1.5	0.5	0.5	0.5
8	15.2	8.9	2.9	1.3
Mean \pm sd	7.58 \pm 6.88	4.5 \pm 4.75	2.36 \pm 3.45	1.25 \pm 2.87
NO ₂ (ppm)	200	120	200	120
ASC (ppm)	550	550	550	550
α -TOC (ppm)	0	0	500	500

TABLE 6
 ESTIMATED "NO EFFECT" LEVELS OF SOME NITROSAMINES

Nitrosamine	No-effect level*	Source
Dimethylnitrosamine	1-2	Terricini et al.
Diethylnitrosamine	1	Druckery et al.
Nitrosopyrrolidine	5	Preussmann et al.

*mg/kg in diet
 (Preussmann et al., 1976)

dicates that NDMA and NDEA were six to seven times more carcinogenic than NPYR, on a molar basis. Typical high and low values of these nitrosamines in food are shown in Table 8. A relative risk factor can then be calculated: $R = PC$, where R = relative risk, P = relative molar potency, and C = concentration in (mol/gm food) $\times 10^{10}$. From the relative risk values in Table 8 it appears that NDMA is five or six times more dangerous than NPYR and a concentration of, for example, 5 ppb NDMA in bacon should be of greater concern than the same amount of NPYR. These calculations assume that the values obtained in test animals can be extrapolated to man. Whether this is true, or not, this concept poses another dimension to the problem of human nitrosamine exposure which has not been considered to this time.

TABLE 7

CARCINOGENIC POTENCY OF NITROSAMINES IN RATS

Nitrosamine	D ₅₀ (m mol/kg)	1/D ₅₀	Relative mol. potency
NDMA	0.0054	185	7
NDEA	0.0065	154	6
NPYR	0.039	26	1

(Archer and Wishnok, 1977)

Possible Consequences of Banning Nitrite

The effects of a ban on nitrite and nitrate can be examined in the experiences in Norway, which introduced such a ban in 1973. Hoyem (1976) reported that: sales of cured meat were reduced about 5% initially but soon returned to normal. Uncolored products, with a statement that no nitrite was added, had to be withdrawn from the market; the consumer

TABLE 8
NITROSAMINES IN PROCESSED MEAT

Nitrosamine	Typical values				Relative risk/g food	
	High		Low		High intake	Low intake
	ppb	mol*	ppb	mol		
NDMA	25	0.34	3	0.04	48	6
NDEA	12	0.12	2	0.02	14	2
NPYR	50	0.50	5	0.05	10	1

*mol $\times 10^9$ /g food
(Archer and Wishnok, 1977)

preferred the pink product when a choice was available. Producers developed some procedures to induce color formation, including: cooking and smoking products without nitrite in the same chamber as products legally containing nitrite, adding nitrite salts to sawdust prior to combustion, storing raw sausages for a few hours to get microbial reduction of natural nitrate, and increasing the nitric oxides in the air in the smokehouse by such means as burning propane gas. There is no serious concern about the shelf-life of the product, and no botulism has been reported even in products where nitrite was completely excluded.

The Council for Agricultural Science and Technology (1978) has prepared an economic assessment of the possible effects of a ban on nitrite. In 1977, about 1.7 billion pounds of bacon were sold. At about \$1.60/lb. this was worth about 2.7 billion dollars. Although some of the meat would be diverted to other products, the addition of losses of cured beef and poultry would increase the total by several billion dollars. The study of medical byproducts from the hog/pork would be curtailed, affecting the health and welfare of millions of people dependent on these products.

Thus, our present state of knowledge suggests that nitrosamines, as a class of compounds, are more prevalent in the environment than previously suspected, and, as a result of increased sensitivity of analytical procedures, detectable at lower levels. Emphasis is gradually being placed on evaluation of the risks involved on exposure to ingested nitrosamines and a clearer picture should emerge in the future.

ABBREVIATIONS USED

NDMA — nitrosodimethylamine; NDMA — nitrosodimethylamine; NDEA — nitrosodiethylamine; NPYR —

nitrosopyrrolidine; NPIP — nitrosopiperidine; NMOR — nitrosomorpholine; NDELA — nitrosodiethanolamine; NSAR — nitrosarcosine.

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