Metabolism of Carcinogenic Nitrosamines by Rat Nasal Mucosa and the Effect of Diallyl Sulfide

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ABSTRACT

Rat nasal cavity is one of the target organs for carcinogenesis induced by N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), and 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The present work investigated the metabolism of these nitrosamines by rat nasal microsomes, as well as the possible modulating factors. Microsomes prepared from rat nasal mucosa were efficient in metabolizing these nitrosamines. In general, the metabolism of the nitrosamines was slightly higher in 9-week-old rats than in 4-week-old animals, and there was no sex-related difference. Fasting of rats for 48 h, which is known to induce hepatic cytochrome P450IIE1 and NDMA metabolism, did not increase the nasal metabolism of NDMA, NDEA, or NNK. Pretreatment of rats with acetone, another inducer of hepatic P450IIH1, did not increase the metabolism of NDMA. Furthermore, it decreased the nasal metabolism of NDEA and NNK. Immunoinhibition studies suggest that, in the nasal mucosa, P450IIH1 is only partially responsible for the oxidation of NDMA and other P450 isoforms are responsible for the metabolism of NDEA. A single p.o. pretreatment of male rats with diallyl sulfide (DAS), a component of garlic oil, caused a significant decrease in the oxidative metabolism of NDEA and NNK in rat nasal mucosa. Whereas the nasal metabolism of NDMA was reduced by DAS pretreatment, there was no change in the amount of the nasal microsomal proteins immunoreactive with the antibodies against P450IIH1. The inhibitory effect of DAS on the nasal oxidative metabolism of NDMA, NDEA, and NNK was also observed in experiments in vitro. The results demonstrate the ability of nasal mucosa to metabolically activate these nitrosamines and the inhibition of this process by DAS, suggesting that DAS may be effective in inhibiting the related nasal tumorigenesis.

INTRODUCTION

NDMA, NDEA, and the tobacco-specific nitrosamine NNK are potent environmental carcinogens (1). It is generally accepted that metabolic activation of these nitrosamines is required for their carcinogenic effects and it occurs via α-hydroxylation by cytochromes P450. Previous work has demonstrated that P450IIH1 is important in the activation of NDMA and other P450 isoforms (2–5). P450IIH1 also metabolizes NDEA efficiently at low substrate concentrations (6). The major P450 isozyme responsible for the metabolism of NNK in nasal mucosa has not been identified, although the involvement of P450IIB1 and P450IAl was suggested (7).

Rat nasal cavity is one of the target organs in experimental carcinogenesis induced by NDMA, NDEA, and NNK (8–11). It is likely that the in situ activation of these nitrosamines plays a critical role in the initiation stage of carcinogenesis. Although nasal mucosa has been found to contain substantial amounts of P450 and NADPH-P450 reductase activity (12, 13), as well as high activity in metabolizing many chemicals including environmental carcinogens (14–18), the identities and properties of P450 isoforms in nasal microsomes are largely unknown. Recently, P450b (11B1) and P450L3a (11E1) have been detected immunohistochemically in the nasal mucosa (13, 19). Two novel nasal P450s, P450olf1 (11G) and P450olfl2 (11H), have been cloned and their functions remain to be established (20, 21).

DAS is a compound derived from garlic (Allium sativum) at 30–100 μg/g of garlic (22). It has been shown to inhibit carcinogenesis induced by several chemical carcinogens, including colon and liver cancers induced by 1,2-dimethylhydrazine, forestomach neoplasia induced by benzo(a)pyrene, and esophageal cancer induced by N-nitrosomethylbenzylamine (23, 24). A recent epidemiological study indicated that the consumption of garlic might be related to reduced risk of stomach cancer (25). Earlier work from our laboratory demonstrated that the inhibition by DAS of metabolic activation of NDMA could be due to the competitive inhibition and inactivation of cytochrome P450IIH1 (26). However, the effects of DAS on the metabolism of NDMA and other carcinogens in nasal mucosa are not known.

In the present work, we studied the metabolism of these nitrosamines by rat nasal microsomes and the factors which affect this process. In order to determine the role of P450IIH1 in the nasal metabolism of NDMA and NDEA, an immunoinhibition study was conducted. We also studied the influence of DAS pretreatment on the metabolism of NDMA, NDEA, and NNK in rat nasal mucosa.

MATERIALS AND METHODS

Chemicals. [14C]NDMA (purity, >99%; 40 mCi/mmol) was synthesized by Stanford Research Institute International (Menlo Park, CA). [3H]HCHO (10 mCi/mmol) with a radioactive purity of >95% was from Du Pont New England Nuclear (Boston, MA). NDEA, NADP+, glucose 6-phosphate, and glucose-6-phosphate dehydrogenase were obtained from Sigma Chemical Co. (St. Louis, MO). [3H]NNK (purity, >98%; 1.1 Ci/mmol) and unlabeled NNK were from Chemssyn Science Laboratories (Lexena, KS). UV standards for NNK metabolites were obtained from Dr. S. Hecht (American Health Foundation, Valhalla, NY). DAS with a purity of 97% was obtained from Aldrich Chemical Co. (Milwaukee, WI). Corn oil was a product of Mazola, CPC International, Inc. (Englewood Cliffs, NJ). The sources for the remaining chemicals, including the reagents for electrophoresis and immunoblot analysis, have been reported previously (27).

Animals and Microsomes. Sprague-Dawley rats were obtained from Taconic Farms (Germantown, NY). Unless otherwise specified, young male rats (90 to 100 g initial body weight) were used. They were maintained in air-conditioned quarters with 12-h light-dark cycles. Acetone (50% solution in water) was given by intragastric intubation.

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: NDMA, N-nitrosodimethylamine; NDEA, N-nitrosodiethylamine; NNK, 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone; NaNal, 4-(methyl nitrosino)-1-(3-pyridyl)-1-butanone; keto alcohol, 4-hydroxy-1-(3-pyridyl)-1-butanone; NNK-N-oxide, 4-(methyl nitrosino)-1-(3-pyridyl)-N-oxide-1-butanone; diol, 4-hydroxy-4-(3-pyridyl)-1-butanol; NNal-N-oxide, 4-(methyl nitrosino)-1-(3-pyridyl)-N-oxide-1-butanone; keto acid, 4-oxo-4-(3-pyridyl)butyric acid; hydroxy acid, 4-hydroxy-4-(3-pyridyl) butyric acid; P450, cytochrome P450; DAS, diallyl sulfide; HPLC, high performance liquid chromatography.

4 Named P450bac or P450j in our previous publications.
at a dosage of 5 ml acetone/kg body weight. For fasting treatment, animals received no food but were given water ad libitum. Control rats received corn oil only. After the treatments (24 h for acetone, 48 h for fasting, and 18 h for DAS), animals were sacrificed, and the nasal mucosa was removed immediately, frozen on dry ice, and stored at −70°C until the preparation of microsomes. To obtain nasal mucosa, skin was removed from the top of the skull and the nose, and then the nasal cavity was opened by splitting the skull sagittally. The nasal mucosa, including respiratory and olfactory epithelium, was stripped from the bone and cartilage of the nasal and paranasal cavities. The turbinate were removed and combined with the rest of the nasal mucosa. Nasal microsomes were prepared by differential centrifugation (2). Previously described methods were used for the determinations of microsomal protein concentration (28), cytochrome P450 content (29), and NADPH-P450 reductase activity, which was measured as the rate of cytochrome c reduction (30).

Nitrosamine Metabolism. The selection of the substrate concentrations used in the metabolism of the nitrosamines was based on the information from our previous work. NDMA metabolism was determined by measuring the production of formaldehyde with a radiometric assay, using a substrate concentration of 40 μM (27). NDEA metabolism was assayed by measuring the formation of acetaldehyde by HPLC, as previously described (31). In brief, the incubation mixture contained, in a total volume of 0.5 ml, 50 mM Tris-HCl (pH 7.4), 10 mM MgCl$_2$, 0.4 mM NADP+, 10 mM glucose 6-phosphate, 0.2 unit of glucose-6-phosphate dehydrogenase, and 10 μM NDMA (1.25 μCi of [5-3H]NDMA). Following incubation, 0.1 ml of 25% ZnSO$_4$ and 0.1 ml of saturated Ba(OH)$_2$ were added to each vial to precipitate protein. Samples were centrifuged and filtered through a 0.45-μm filter (Gelman Sciences, Ann Arbor, MI) prior to HPLC analysis. Separation and quantitation of NNK metabolites were performed by reverse phase HPLC, using a Waters UV detector and a Radiomatic Beta Flo-One radioflow detector. A Waters Bondapack C$_8$ column (3.9-mm i.d. diameter x 300-mm length) was eluted with a linear gradient of 95% buffer A (0.02 M sodium phosphate, pH 7.0) to 65% buffer A/35% methanol, over a 50-min period. The identities of the metabolites were established by coelution with authentic UV standards.

Immunoinhibition Studies. The following antibodies were used for the immunoinhibition studies: monoclonal 1-91-3 (anti-P450IIE1), BE52 (anti-P450IIB1/1IB2), and C8 (anti-P450IAl) and polyclonal Anti-j (anti-P450IIE1) and Anti-a (anti-P450IJA1). These antibodies have been shown to inhibit the specific activities of the corresponding P450 isozymes (5, 33–35). Nasal microsomes were preincubated with antibodies at room temperature for 15 min before the initiation of the reactions by addition of the substrates. The metabolites from NDMA and NDEA metabolism were then analyzed after the reaction.

Immunoblot Analyses. Antibodies against P450IIB1 were kindly provided by Dr. F. Gonzalez (National Cancer Institute, Bethesda, MD), and antibodies against P450IIE1 were prepared as described (4). Immunoblot analysis with these two antibodies was performed as previously described (27). A Shimadzu dual-wavelength thin layer chromatography scanner (model CS-930) was used for the densitometric measurement.

Statistical Analysis. Student’s t test or one-way analysis of variance was used for statistical treatment.

**RESULTS**

Metabolism of Nitrosamines in Nasal Microsomes. Nasal microsomes from untreated rats had a moderate level of NDMA demethylation activity, comparable to that of kidney microsomes (data not shown); a fairly high level of NDEA deethylation activity, comparable to that in liver microsomes (31); and high activity in the metabolism of NNK (Tables 1 and 2). Using the same amount of microsomal protein and under the same incubation conditions, about 90% of the NNK was metabolized by rat nasal microsomes, whereas the microsomes from rat lung, a major target organ for NNK, converted only about 5% of NNK to its metabolites (Fig. 1). Under the present incubation conditions, keto alcohol, a metabolite from the α-hydroxylation of NNK, was the major product. NNK-N-oxide, a product of pyridine N-oxidation (detoxification pathway), was formed in small quantity. NNAL, a major metabolite observed in NNK metabolism by liver and lung microsomes, due to a reductive pathway, was not detected, but its secondary metabolite NNAL-N-oxide was observed. Other secondary metabolites, hydroxy acid, keto acid, and diol, were formed in rather large quantities. These incubation conditions were used in most studies so that
Results

Effects of Age and Sex. The ability of nasal mucosa to metabolize the carcinogenic nitrosamines was examined in rats of different age and sex. In general, nasal microsomes prepared from 9-week-old rats had a slightly higher activity in metabolizing NDMA, NDEA, and NNK than the microsomes from 4-week-old rats (Tables 1 and 2). Similarly, NADPH-P450 reductase activity was also higher in the nasal microsomes from 9-week-old rats (Table 1). There was no significant sex-related difference in the nasal metabolism of NDMA, NDEA, and NNK in rats (Tables 1 and 2).

Effects of Fasting and Acetone. Neither fasting nor acetone pretreatment caused a significant increase in the nasal metabolism of NDMA (Table 3), which is different from their effect on hepatic and renal NDMA metabolism, in which at least a 2-fold induction was observed (36, 37). Whereas fasting did not change the ability of nasal microsomes to metabolize NDMA, acetone pretreatment decreased the nasal metabolism of NDEA to 12% of the control value (Table 3). In the metabolism of NNK by nasal microsomes, there was no difference between the 48-h fasted and the control animals (Table 4). Acetone pretreatment caused a significant reduction in the nasal metabolism of NNK, with about a 65% decrease in the formation of NNK-N-oxide and keto alcohol, as well as a more pronounced decrease (89 to 100%) in the formation of the secondary metabolites.

The induction of NDMA demethylation by fasting or acetone in rat liver and kidney microsomes is due to an increase in the level of P450IIIE1 (36, 37). To examine whether the P450IIIE1 level in nasal microsomes was affected by fasting or acetone, an immunoblot analysis using the anti-P450IIIE1 IgG (4) was performed. As shown in Fig. 2, top, there were two immunoreactive protein bands detected in the immunoblot; one band comigrated with the P450IIIE1 standard (designated as band 1) and the other one with a slightly lower molecular weight (designated as band 2). In the nasal microsomes prepared from control (Fig. 2, top, lane 6) and fasted (Fig. 2, top, lane 5) rats, band 1 was hardly detectable, while band 2 was the major immunoreactive protein. However, acetone pretreatment, in rats fed either with lab chow (Fig. 2, top, lane 7) or with a semisynthetic diet (Fig. 2, top, lanes 2 and 4), significantly decreased the level of band 2 but increased the level of band 1. Neither fasting nor acetone pretreatment significantly altered the P450IIIB1 level in rat nasal microsomes, as determined by immunoblot analysis using the anti-P450IIIB1 IgG (Fig. 2, bottom).

Immunoinhibition Studies. Previous work has demonstrated that P450IIIE1 is the major enzyme in the metabolic activation of NDMA in rat liver, displaying a low Km for NDMA demethylation (2-6). Hepatic P450IIIE1 also metabolizes NDEA efficiently at low substrate concentrations (6). To further examine the involvement of P450IIIE1 in the metabolism of NDMA and NDEA in rat nasal microsomes, immunoinhibition studies with 1-91-3, a monoclonal antibody (33), and Anti-j, polyclonal

![Fig. 1. HPLC profiles of NNK metabolism by rat lung and nasal microsomes. The microsomes were prepared from untreated animals (pooled from four rats). Reactions were carried out for 30 min at 37°C, using 0.2 mg of microsomal protein and 10 µM NNK (1.25 µCi of [5-3H]NNK). A, NNK metabolism by lung microsomes; B, NNK metabolism by nasal microsomes.](image-url)
monospecific antibodies (5) against P450IIIE1, were conducted. Rat kidney microsomes were selected as a positive control. The titration curve using different amounts of these two antibodies (ranging from 50 to 500 μg protein) indicated that the maximal inhibitory effect on nasal NDMA metabolism was obtained when the amount of the antibodies was approximately 100 μg of protein (data not shown). The presence of 100 μg of 1-91-3 or Anti-j in the incubation caused a 100 and 86% inhibition of NDMA metabolism by rat renal microsomes, respectively (Table 5). However, under the same incubation conditions, the inhibitory antibodies resulted in less than 50% inhibition of the NDMA metabolism by rat nasal microsomes (Table 5). Anti-j had no inhibitory effect on the nasal metabolism of NDEA. Inhibitory antibodies against P450 isozymes IIB1/IIB2, IIA1, and IA1 failed to inhibit the nasal metabolism of NDMA and NDEA (data not shown).

Influence of DAS Pretreatment on Nasal Nitrosamine Metabolism. DAS pretreatment decreased the nasal metabolism of NDMA and NDEA to 21 and 4% of the control values, respectively (Table 6). In the nasal metabolism of NNK, DAS pretreatment caused a significant inhibition of the formation of the oxidative metabolites, with a 93% decrease in keto alcohol and 99–100% decrease in the other NNK oxidative metabolites (Table 7). However, DAS pretreatment increased the formation of NNAL (Table 7), a reductive metabolite. The percentage of unmetabolized NNK was 13% in the control group and increased to 93% in the DAS group. The extensive inhibition of the oxidative pathways may enhance the formation of NNAL by increasing the substrate availability for the reductive pathway.

Pretreatment of rats with DAS has been found to decrease the level of P450IIIE1 and increase P450IIIB1 in liver microsomes (26). Immunoblot analysis of the nasal microsomes prepared from the control and DAS-treated rats revealed that the major protein that was immunoreactive with the antibodies against P450IIIE1 was band 2, while band 1 was almost nondetectable (data not shown), consistent with the immunoblot analysis of the control microsomes shown in Fig. 2. Densitometric measurement indicated that there was no change in the level of band 2 in the nasal microsomes from DAS-treated rats, and the induction effect of DAS on the amount of P450IIIB1 was not observed in the nasal microsomes (data not shown).

In Vitro Inhibition of Nitrosamine Metabolism by DAS. To further understand the inhibitory action of DAS pretreatment on nasal nitrosamine metabolism, DAS was added to the incubation system containing different nitrosamine substrates and nasal microsomes prepared from the untreated rats. The addition of DAS (0.05 to 1 mM) caused a dose-dependent inhibition of the metabolism of NDMA by nasal microsomes, showing a 60% inhibition at 1 mM DAS (data not shown). At 1 mM DAS, NDEA metabolism was inhibited by 26%. In NNK metabolism, a dose-dependent inhibition was also observed (Table 8). The formation of the secondary metabolites was inhibited to a greater extent than the formation of keto alcohol or NNK-N-oxide. Addition of DAS increased the production of NNAL, similar to the effect observed in vivo (Table 7).

Table 7 Effect of DAS pretreatment on rat nasal microsomal NNK metabolism

<table>
<thead>
<tr>
<th>NNK metabolite (pmol)</th>
<th>Hydroxy acid</th>
<th>Keto acid</th>
<th>NNAL-N-oxide</th>
<th>Diol</th>
<th>NNAL-N-oxide</th>
<th>Keto alcohol</th>
<th>NNAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27.0 ± 4.8</td>
<td>768 ± 180</td>
<td>21.0 ± 4.2</td>
<td>51.0 ± 8.4</td>
<td>22.8 ± 1.2</td>
<td>3204 ± 66</td>
<td>&lt;1</td>
</tr>
<tr>
<td>DAS</td>
<td></td>
<td></td>
<td></td>
<td>&lt;1*</td>
<td></td>
<td>228 ± 84*</td>
<td>57.0 ± 3.0*</td>
</tr>
</tbody>
</table>

*P < 0.01 in comparison with the control group.
The present study demonstrates that microsomes prepared from rat nasal mucosa can catalyze the metabolism of NDMA, NDEA, and NNK. This is consistent with previous reports on nitrosamine metabolism by nasal tissues, such as NNK metabolism by cultured nasal septum explant (38) and NDEA metabolism studied by whole-body autoradiography (17). Recently, the metabolism of NDEA by nasal microsomes from hamsters, rats, and humans has been reported by Longo et al. (39, 40). However, the reported activity (nmol acetdehyde formed/min/mg microsomal protein) for NDEA deethylation at a substrate concentration of 50 mM was much lower than (only about 10% of) that found in the present study using 1 mM NDEA. The discrepancy could be due to the assay conditions, particularly the capping of the test tubes during the incubation and the addition of the trapping agent semicarbazide at the end of the incubation. We found that capping the test tubes minimized the loss of acetdehyde through evaporation and the addition of semicarbazide before the completion of the incubation significantly inhibited the metabolism of NDEA (data not shown). However, other factors, such as sample preparation, may also be involved in the discrepancy. We noticed that the nasal glutathione S-transferase activity reported by Longo et al. (41) was also significantly lower than that found in our laboratory. In the nasal metabolism of NNK, NNAL, a metabolite from the carbonyl reduction of NNK, was not detected. This agrees with the result of a previous report in which NNK metabolism was studied using cultured rat nasal mucosa explants (38). Belinsky et al. (42) observed that, in rat nasal mucosa, NNK-induced O^-methylguanine was 4 times higher in the respiratory than in the olfactory epithelium, suggesting that NNK could be more actively metabolized by the respiratory mucosa. Due to the limited amount of nasal mucosa available for the microsome preparation, we did not separate these two epithelia, and NNK metabolism by these two different epithelia remains to be studied.

In general, the metabolism of NDMA, NDEA, and NNK by nasal microsomes was slightly higher in 9-week-old rats than in 4-week-old rats. In contrast to NDMA metabolism in mouse kidney (27), a sex-related difference in the nasal metabolism of NDMA, NDEA, and NNK was not observed. Fasting and acetone pretreatment have been found to induce hepatic and renal NDMA metabolism in rats (36, 37). Acetone pretreatment has also been shown to induce NDEA metabolism in rat liver (31, 43). However, in the present study, 48-h fasting had no effect on the nasal metabolism of NDMA, NDEA, and NNK (Tables 3 and 4). In the acetone-treated rats, there was no increase in the nasal metabolism of NDMA but a significant decrease in both NDEA and NNK metabolism by the nasal microsomes. The differential effects of acetone pretreatment suggest that the metabolism of these nitrosamines in the nasal mucosa is catalyzed by different P450 isozymes.

The less than 50% inhibition of nasal NDMA metabolism by the two P450IIE1-specific antibodies indicated that P450 isoforms other than P450IIE1 may be involved in the nasal metabolism of NDMA at low substrate concentrations (40 /KM), although the possibility that the incomplete inhibition may be due to the different topology of P450IIE1 in the nasal microsomes cannot be excluded. The inability of Anti-j to inhibit nasal NDEA metabolism is consistent with the differential effect of acetone on the nasal NDMA and NDEA metabolism and further suggests that nasal metabolism of NDEA is not catalyzed by P450IIE1.

Immunoblot analysis using antibodies against rat hepatic P450IIE1 revealed two immunoreactive bands. The exact nature of these two bands is not clear. Band 1 comigrated with the P450IIE1 standard (M, 52,000) and was barely detectable in the nasal microsomes from the control, fasted, and DAS-treated animals. The low level of band 1 in the rat nasal microsomes and its induction by acetone seem consistent with the observations that P450LM3a (IIE1) was less than 1% of the total P450 in rabbit nasal mucosa (44) and was elevated about 6-fold in rabbit olfactory mucosa after acetone treatment (45). Recently, Ding and Coon (46) purified two major nasal P450 isoforms, P450NMa (M, 49,500) and P450NMb (M, 51,000), from the rabbit nasal mucosa and reported that P450NMa had very high activity in the deethylation of NDEA. They also reported that their previously used anti-P450LM3a (IIE1) antibodies cross-reacted with P450NMa and NMb (45). Judging from the molecular weight and the relative abundance in the nasal microsomal proteins, it is possible that band 2 represented P450NMa, and the detection by the antibodies against P450IIE1 could be due to the immuno-cross-reactivity. The concomitant decrease in the intensity of band 2 and NDEA metabolism in nasal microsomes by acetone pretreatment also favors this hypothesis. In DAS-treated rats, the significant decrease in nasal NDEA metabolism was not accompanied by a change in the intensity of band 2, probably due to the inactivation of this enzyme by DAS. Nevertheless, the nature of these two P450IIE1-immunoreactive bands and their role in the metabolism of nitrosamines remain to be studied.

The mechanisms of the presently observed inhibitory effects of DAS on the oxidative metabolism of NDMA, NDEA, and NNK are not known. They could be due to decreases in the amounts of enzymes responsible for the metabolism, as demonstrated for the hepatic NDMA metabolism (26), but this point remains to be substantiated. The observed inhibitory effect of DAS in vitro suggests that the lower metabolic activity in nasal mucosa from DAS-treated rats could be at least partially attributed to the residual DAS in the microsomes. The

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**Table 8** In vitro inhibition of nasal NNK metabolism by DAS

<table>
<thead>
<tr>
<th>DAS (mM)</th>
<th>Hydroxy acid</th>
<th>Keto acid</th>
<th>NNAL-o-oxide</th>
<th>Diol</th>
<th>NNAL-o-oxide</th>
<th>Keto alcohol</th>
<th>Unmetabolized NNK (pmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28.5</td>
<td>633</td>
<td>24.3</td>
<td>45.9</td>
<td>19.2</td>
<td>1230</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0.05</td>
<td>25.8</td>
<td>435</td>
<td>24.6</td>
<td>37.8</td>
<td>18.3</td>
<td>1266</td>
<td>24.3</td>
</tr>
<tr>
<td>0.2</td>
<td>10.2</td>
<td>168</td>
<td>11.7</td>
<td>14.4</td>
<td>14.1</td>
<td>1074</td>
<td>30.0</td>
</tr>
<tr>
<td>1.0</td>
<td>8.7</td>
<td>66</td>
<td>&lt;1</td>
<td>12.0</td>
<td>10.2</td>
<td>738</td>
<td>43.5</td>
</tr>
</tbody>
</table>

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5 Z. Guo et al., unpublished observations.
actual levels of residual DAS in the microsomal preparation, however, remain to be determined.

In addition to the alkylating species, the formaldehyde and acetaldehyde produced in the metabolism of NDMA and NDEA are nasal carcinogens (47, 48). In a recent study, a long-term inhalation exposure to low dose (0.2 ppm) NDMA caused an 86% nasal tumor incidence in rats (49). The existence of high activity in rat nasal mucosa for metabolizing NDMA, however, remain to be determined.

References


5. Thomasson, E.R., Bartsch, H., and Ninnemann, K. High activity in rat nasal mucosa for metabolizing NDMA, however, remain to be determined.


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