Long-Term Exposure to Ozone Increases Acute Pulmonary Centriacinar Injury by 1-Nitronaphthalene: II. Quantitative Histopathology

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ABSTRACT

Long-term exposure to the oxidant air pollutant ozone (O₃) is associated with tolerance to the acute effects of oxidant injury. To test whether this resistance to acute injury extends to bioactivated pulmonary toxicants, male Sprague-Dawley rats were exposed to filtered air (FA) or 0.8 ppm O₃ (8 h/day) for 90 days and administered 1-nitronaphthalene i.p. at doses of 0, 50, or 100 mg/kg. 1-Nitronaphthalene is a pulmonary cytotoxicant requiring metabolic activation. High-resolution histopathology, transmission electron microscopy, and morphometry revealed significantly greater 1-nitronaphthalene toxicity in the central acinar region of O₃-exposed rats compared with FA-exposed rats. At 100 mg/kg, injury to terminal bronchioles in O₃-exposed rats involved denudation of 86% of the basement membrane; 78% of the cells remaining on the epithelium were necrotic. This is compared with denudation of 4% of the basement membrane of FA-exposed rats administered 100 mg/kg 1-nitronaphthalene; only 25% of the cells remaining on the epithelium were necrotic. The key difference between FA- and O₃-exposed rats treated with 1-nitronaphthalene was the heightened severity of ciliated cell toxicity in O₃-exposed animals. This is despite the fact that long-term exposure to ozone produces tolerance to oxidant stress in the epithelium of the central acinus. No differences in the susceptibility of intrapulmonary airways or trachea to 1-nitronaphthalene were observed between filtered air- and ozone-exposed rats. This study demonstrates a site-selective synergy between the copollutants ozone and 1-nitronaphthalene in the production of acute lung injury.

Ambient air in urban areas over much of the United States contains a complex mixture of oxidants and hydrocarbons that arise from automobile emissions; particulate matter from combustion and arid farming conditions; and industrial emissions of solvents, heavy metals, and acids. The oxidant air pollutant ozone, to which nearly 100 million Americans in 38 metropolitan areas are exposed at concentrations exceeding the 1-h National Ambient Air Quality Standard of 0.12 ppm (U.S. Environmental Protection Agency, 1999: USA Air Quality Nonattainment Areas; http://www.epa.gov/airs/non-attn.html), is only one component of this milieu. Nevertheless, little is known about whether exposure to ozone alters the response of the respiratory system to other classes of toxicants found as copollutants.

Ozone has been studied in combination with other reactive gases such as sulfur dioxide and sulfuric acid aerosols. These studies found that short-term combination exposures to ozone and sulfuric acid produce significant increases in the rate of synthesis of lung collagen and increases in the number of fibroblasts (Last et al., 1984). Long-term exposures to both sulfuric acid and ozone result in secretory cell hyperplasia in conducting airways (Schlesinger et al., 1992), which attenuates with no lasting morphological change when the exposure period is lengthened (Moore and Schwartz, 1981). Although the long-term consequences of combination exposures are unclear, these studies collectively support the concept of synergy between gaseous copollutants when exposure is simultaneous.

Prolonged exposure to a toxicant can result in tolerance to further acute injury and inflammation. For example, repeated exposures to ozone (Paige and Plopper, 1999) or naphthalene (O’Brien et al., 1989; Lakritz et al., 1996) are associated with development of tolerance to acute injury. Short-term exposure to ozone injures ciliated bronchiolar and alveolar type I epithelial cells, producing characteristic lesions in the central acinus, whereas long-term exposure to ozone results in biochemical changes that render the epithelium resistant to further oxidant injury. These changes include increases in activity of a number of antioxidant en-

ABBREVIATION: 1-NN, 1-nitronaphthalene.
zymes (Plopper et al., 1994) and in levels of glutathione (Duan et al., 1996). Studies on alterations in pulmonary P450 activity by long-term exposure to ozone are difficult to interpret. Cytochrome P450 1A1 activity, for example, has been reported to increase (Takahashi et al., 1985; Takahashi and Miura, 1987, 1989) or decrease (Riotjens et al., 1988) after ozone exposure. Further complicating interpretation is the fact that these activity measurements were made in micromesomes prepared from homogenates of whole lung and therefore were likely insufficiently sensitive to detect regional and subcompartment differences in activity. This leaves open the question of whether the tolerance to ozone developed with long-term exposure also confers tolerance to bioactivated toxicants found in polluted ambient air.

To address this issue we used a model of long-term ozone exposure, which renders all target sites within the respiratory system resistant to further injury by ozone, followed by a single exposure to 1-nitronaphthalene (1-NN), a toxicant bioactivated by the cytochrome P450 monoxygenase system. 1-Nitronaphthalene is an atmospheric reaction product of naphthalene and nitrogen pentoxide (Pitts et al., 1985; Pitts, 1987). Nitronaphthalenes constitute the single largest genotoxic fraction of polluted ambient air (Gupta et al., 1996); the genotoxicity of nitronaphthalenes is dependent upon P450 activation (Grosovsky et al., 1999). Systemic administration of 1-nitronaphthalene results in well characterized acute necrosis of airway epithelium (Johnson and Riley, 1984; Rasmussen et al., 1986; Sauer et al., 1995, 1997; Paige et al., 1997). Previous studies suggest that cytochrome P450 monooxygenase 2B contributes to pulmonary injury from 1-nitronaphthalene (Verschoyle et al., 1993). In the companion study (Paige et al., 2000), we found that the rate of formation of 1-nitronaphthalene metabolites was significantly increased in the distal (central acinar) lung subcompartment of ozone-compared with filtered air-exposed rats. This focal increase in the rate of 1-nitronaphthalene metabolism corresponded with increased P450 2B protein expression and activity in the same lung subcompartment. No changes in expression or activity were observed in intrapulmonary airways or trachea.

We tested the hypothesis that long-term exposure to ozone, despite enhanced antioxidant enzyme activities and intracellular glutathione, does not confer resistance to the bioactivated toxicant 1-nitronaphthalene.

**Materials and Methods**

Animals, animal care, and ozone exposures used in these studies are identical to those described in the companion study (Paige et al., 2000).

**1-Nitronaphthalene Treatment.** After the 90-day exposure, ozone- (O3) and filtered air (FA)-exposed rats were treated with 50 or 100 mg/kg 1-NN in corn oil by single intraperitoneal injection (injection volume less than 1 ml). Controls received the same volume of 100 mg/kg 1-NN in corn oil by single intraperitoneal injection (injection volume less than 1 ml). Controls received the same volume of

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#### Tissue Processing for Histopathology.

Animals were killed 24 h after injection by an overdose of sodium pentobarbital. The lungs were fixed for 1 h via tracheal cannula with glutaraldehyde/paraformaldehyde in cacodylate buffer (330 mOsm, pH 7.4) at 30 cm of fluid pressure. The lungs were removed from the chest and the left lobe was grossly dissected before embedding. Lung sections were fixed with 1% osmium tetroxide, poststained with uranyl acetate, dehydrated in ethanol, infiltrated with propylene oxide, and embedded in Araldite 502. Blocks were cut into 0.5-μm-thick sections with glass knives on a Zeiss Microm HM540 and stained with toluidine blue.

#### Tissue Selection for Histopathology.

Airway generations were anatomically defined to ensure that comparisons within the airway tree were valid. The lower two-thirds of the trachea was embedded whole and the region immediately proximal to the carina was sectioned. Cross sections of trachea were mounted such that each slide showed a complete profile of both cartilaginous and muscular regions. To evaluate the extent of injury within the intrapulmonary airways, the first ventral branch off the axial pathway was evaluated on slides containing the axial pathway of the left lobe in cross-section with several generations of the branch visible (Paige et al., 1997). Terminal bronchioles were defined as the generation immediately proximal to the first alveolar outpocketing. Only terminals in longitudinal section (with the central acinus visible) were used.

To evaluate injury, sections were screened blind and grouped by severity of injury. Parameters used for evaluation of epithelial injury based on our previous study (Paige et al., 1997) were cell vacuolation (nonciliated generally preceding ciliated) and exfoliation. The least severe injury involved vacuolation of only one cell type (nonciliated) and squamation of the remaining epithelium with few regions of exposed basement membrane, whereas the most severe injury involved extensive vacuolation and exfoliation of both cell types with focal denudation of the basement membrane (confirmed by transmission electron microscopy).

#### High-Resolution Light Microscopy.

High-resolution light video images were captured using a DAGE MTI VE1000 video camera (Michigan City, IN) mounted on a Zeiss Axioscope MC80 with a 63× oil immersion lens. The camera was interfaced with a Macintosh Centris 650 running NIH Image software. Labels and magnification bars were added in Adobe Photoshop (Adobe Systems, San Jose, CA) and final images were printed on a Codonics NP-1600.

#### Transmission Electron Microscopy.

Thin sections (60 to 90 nm) were produced with a diamond knife on an LKB Nova ultramicrotome. Serial sections were stained with uranyl acetate and lead citrate, and examined with a Zeiss EM10 at 80 kV.

#### Morphometry.

The thickness and relative abundance of terminal bronchiolar epithelial cells were evaluated by procedures that are discussed in detail elsewhere (Hyde et al., 1990, 1991; Plopper et al., 1994). All measurements were made using high-resolution light microscopy (63× oil immersion objective and 0.5-μm sections) as described above. The analysis was performed using a cycolid grid overlay and software for counting points and intercepts (Stereology Toolbox, Davis, CA) (for detailed description of grids and counting procedures, see Hyde et al., 1990, 1991). The percentage volume density, Vₚ, the proportion of the epithelium composed of ciliated, nonciliated, and necrotic cells was determined by point counting and calculated using the following formula:

\[ Vₚ = Pₚ = Pₚ/P₁ \]

where \( Pₚ \) is the point fraction of \( P₁ \), the number of test points hitting the structure of interest, divided by \( P₁ \), the total points hitting the reference space (epithelium). The volume of epithelium of the cell type of interest per unit of basement membrane (\( S_L \)) was determined by point and intercept counting and was calculated using the following formula:

\[ S_L = 2 I/J \]

| Table 1 |
|------------------|------------------|------------------|
| **Number of rats per treatment group** | **Dose 1-NN** | **FA-Exposed** | **O₃-Exposed** |
|------------------|------------------|------------------|
| 0 mg/kg | 8 | 12 |
| 50 mg/kg | 11 | 15 |
| 100 mg/kg | 11 | 21 |
where $I_o$ is the number of intercepts with the object (epithelial basal lamina) and $L_r$ is the length of test line in the reference volume (epithelium). To determine thickness of the epithelium, a volume per unit area of basal lamina ($\mu^3/\mu^2$) was then calculated using the following formula for arithmetic mean thickness ($\tau$):

$$\tau = \frac{V_v}{S_v}$$

Epithelium for the terminal bronchiole was defined as the epithelium just proximal to the first alveolar outpocketing. At least four fields of terminal bronchiolar epithelium were taken from each of three animals evaluated per exposure group.

**Statistics.** Data were imported into StatView (Abacus Concepts, Berkeley, CA) for ANOVA and Bonferroni/Dunn post hoc analysis of differences between mean body weights of exposure and dose groups before treatment. For morphometry of terminal bronchioles, values calculated on a per animal basis from counts made on at least four fields per animal were used to calculate the mean and standard deviation for each exposure group (at least three animals per expo-

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**Fig. 1.** Low-magnification light micrographs of central acinar region from filtered air- (A, C, and E) and ozone- (B, D, and F) exposed rats administered 0 (A and B), 50 (C and D), or 100 mg/kg (E and F) 1-nitronaphthalene. Alveolar macrophages (arrows) are more abundant in the central acinus of ozone-exposed compared with filtered air-exposed animals. Brackets indicate area shown in detail in Fig. 3. Scale bar, 100 $\mu$m.
sure group). Differences between group values were assessed by ANOVA. Significance was determined by Bonferroni/Dunn post hoc analysis at $P < .05$.

**Results**

Nine of 21 ozone-exposed rats administered 100 mg/kg 1-NN died within 24 h of treatment; cause of death was not determined. Gasping, indicating respiratory distress, was a common observation in moribund animals. No deaths were observed at any other dose in either exposure group.

**Parenchyma.** High-resolution light microscopic examination did not identify injury in alveolar type I or type II epithelial cells. The most notable difference in the centriacinar region between ozone- and filtered air-exposed animals was a variable increase in the abundance of alveolar macrophages (Fig. 1). Injury in the parenchyma in both ozone- and filtered air-exposed animals administered 50 or 100 mg/kg 1-NN was evident by transmission electron microscopy. Type I cell injury, characterized by membrane bound vacuoles in the cytoplasm (Fig. 2), was diffuse and not localized to the central acinus. Areas of septal thickening in ozone-exposed animals did not appear to be more susceptible to injury. The frequency of injured type I cells appeared to be greater at 100 mg/kg than at 50 mg/kg in both filtered air- and ozone-exposed animals, but did not appear to differ between filtered air- and ozone-exposed animals.

**Terminal Bronchioles.** In carrier (corn oil)-treated, filtered air-exposed animals (Fig. 3A), terminal bronchiolar epithelium consisted of a uniform layer of ciliated and nonciliated cells whose thickness was approximately twice the diameter of an epithelial cell nucleus. Cilia extended into the airway lumen and granules were visible in the apical projections of the nonciliated cells. Debris and inflammatory cells were rarely observed in the lumen. Total epithelial thickness ($t$) (Fig. 4A), bronchiolar epithelial mass ($S_e$) of ciliated (Fig. 4B) and nonciliated cells (Fig. 4C), and the proportion of epithelium ($V_e$) composed of ciliated (55–65%) (Fig. 5A) or nonciliated cells (34–45%) (Fig. 5B) were not significantly different between filtered air- and ozone-exposed, carrier-treated animals. No necrotic epithelial cells were observed in filtered air exposed animals, and less than 1% of epithelial cells in ozone-exposed animals was necrotic (Fig. 5C).

![Fig. 2. Transmission electron micrograph illustrating membrane-bound vacuoles found in alveolar type I cells (closed arrows) of 1-nitronaphthalene-treated animals. There is swelling around a capillary (arrowhead), and a neutrophil is visible migrating through the interstitial fibroblast layer (open arrow). This micrograph additionally illustrates the abundant alveolar and interstitial macrophages (M) associated with chronic ozone exposure. Original magnification 2000×; scale bar, 6 μm. The area in brackets is shown in higher magnification in the inset (original magnification 4000×; scale bar, 1 μm).](image-url)
The primary difference between 0 mg/kg and treatment with 50 mg/kg 1-NN was a loss of nonciliated cells. In ozone-exposed animals treated with 50 mg/kg 1-NN, injury involved exfoliation of both ciliated and nonciliated cells. Many of the remaining cells appeared rounded with pyknotic nuclei (Fig. 3D). There was no significant difference in total epithelial thickness (Fig. 4A) between filtered air- and ozone-exposed animals. In both filtered air- and ozone-exposed rats after treatment with 50 mg/kg, the proportion of epithelial volume composed of nonciliated cells (Fig. 5B) was significantly decreased ($P < .05$) and the proportion of epithelial volume composed of ciliated cells was increased (Fig. 5A) relative to 0 mg/kg 1-NN (difference not significant); bronchial epithelial composition was not different between filtered air- and ozone-exposed animals. Nonciliated cell mass (Fig. 4C) was significantly decreased ($P < .05$) and ciliated cell mass (Fig. 4B) was increased (difference not significant) in both filtered air- and ozone-exposed rats after treatment with 50 mg/kg 1-NN. In filtered air-exposed animals, the epithelium remained continuous and 6% of the cells on the epithelium were necrotic (Fig. 5C). In ozone-exposed animals treated with 100 mg/kg 1-NN, there were few to no remaining nonciliated cells and the remaining ciliated cells were squamated. The epithelium remained continuous with patches of exfoliation and focal denudation (Fig. 3E) as confirmed by transmission electron microscopy (Fig. 6). Ozone-exposed animals exhibited far greater injury after treatment with 100 mg/kg 1-NN. This was characterized by exfoliation of much of the epithelium such that large portions of the basement membrane were denuded. At 100 mg/kg, the total epithelial thickness of ozone-exposed animals was significantly decreased ($P < .05$) relative to filtered air-exposed animals administered 100 mg/kg (Fig. 4A). There was a significant decrease ($P < .05$) in the proportion of epithelium composed of ciliated cells in ozone-exposed animals treated with 100 mg/kg 1-NN, relative to filtered air-exposed animals (Fig. 5A). In ozone-exposed animals, the proportion of epithelium composed of ciliated cells (20%) was decreased to one-third the value of ozone-exposed, carrier-treated animals (65%). This corresponds with a 5-fold decrease in ciliated cell mass in ozone-exposed, relative to filtered air-exposed animals (Fig. 4B). In filtered air-exposed animals treated with 100 mg/kg 1-NN, 4% of the basement membrane was denuded and 25% of the cells remaining on the epithelium were necrotic (Fig. 5C). In ozone-exposed animals treated with 100 mg/kg 1-NN, 87% of the basement membrane was denuded (significantly different from filtered air-exposed animals treated with 100 mg/kg, $P < .001$) and 78% of the cells remaining on the epithelium were necrotic (Fig. 5C) (not significant, $P = .0501$).

**Intrapulmonary Airways.** Intrapulmonary airways in filtered air- and ozone-exposed animals administered 0 mg/kg 1-NN were lined by a continuous epithelium composed of ciliated and nonciliated cells, with cilia and apical surfaces of nonciliated cells projecting into the airway lumen (Fig. 7, A and B). There were no discernable differences between ozone- and filtered air-exposed animals treated with 50 mg/kg 1-NN (Fig. 7, C and D). At this dose, the epithelium was composed almost entirely of ciliated cells and a few necrotic, nonciliated cells. There were also focal areas of ciliated cell vacuolation. At 100 mg/kg, there were focal areas of exfoliation and de-
nudation adjacent to sections of squamated ciliated cells (Fig. 7, E and F). There was considerable regional variability in response within the intrapulmonary airways with proximity to branch points and blood vessels. The variability within the intrapulmonary airways required screening of large numbers of slides; a minimum of two slides containing intrapulmonary airways was screened for each animal of the above-mentioned treatment groups. There was no discernable difference in the severity of injury between filtered air- and ozone-exposed rats administered 1-NN.

Trachea. In filtered air- and ozone-exposed animals treated with corn oil, the tracheal epithelium was a mixture of columnar ciliated and nonciliated cells, and low-profile basal cells (Fig. 8, A and B). The distribution of cell types and the thickness of the epithelial layer varied from cartilaginous to muscular regions of the trachea. Nonciliated and basal
cells were vacuolated after treatment with 50 mg/kg 1-NN, with some focal areas of exfoliation (Fig. 8, C and D). At 100 mg/kg 1-NN, ciliated cells were also necrotic and exfoliated, leaving large portions of the epithelium denuded (Fig. 8, E and F) (confirmed by transmission electron microscopy). Similar to intrapulmonary airways, the response was variable by region and proximity to blood supply. There were no discernable differences between filtered air-exposed and ozone-exposed tracheas.

**Discussion**

Human populations are exposed to both oxidant gases and bioactivated toxicants, and prolonged exposure to either class of toxicant can result in tolerance to further acute injury and inflammation as, for example, with ozone (Paige and Plopper, 1999) or naphthalene (O’Brien et al., 1989; Lakritz et al., 1996). What is poorly understood is how tolerance to an oxidant gas such as ozone influences the biological re-

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**Fig. 6.** Representative transmission electron micrograph showing denudation of the basement membrane (arrowheads) after treatment with 1-NN. Original magnification, 2000×; scale bar, 5 μm.

**Fig. 7.** Light micrographs of representative regions of intrapulmonary airways from rats exposed to filtered air (A, C, and E) or 0.8 ppm ozone (B, D, and F) for 90 days and then administered 1-NN at doses of 50 mg/kg (C and D) or 100 mg/kg (E and F). Corn oil controls (0 mg/kg 1-NN) are also shown (A and B). Scale bar, 20 μm.
sponse to a bioactivated toxicant. Numerous studies have addressed the effects of ozone on pulmonary P450 activity, but few have used sampling methods sufficiently sensitive to address regional differences in activity within the lung. The companion study (Paige et al., 2000) determined CYP 2B and NADPH reductase activity in specific subcompartments of the lung, including the primary target site for acute ozone injury, the central acinus. The significant increase in microsomal CYP 2B activity in ozone-exposed rats was associated only with the central acinus; activity in other lung subcompartments and the liver was not different from that in filtered air-exposed animals. This correlated with a significant increase in the rate of 1-nitronaphthalene metabolism in the distal region of the lung (including the central acinus) after long-term exposure to ozone. The present study determined whether tolerance to ozone confers resistance to the metabolically activated toxicant 1-nitronaphthalene. As might be anticipated based on elevated CYP 2B activity and elevated rates of metabolism of 1-nitronaphthalene in the distal region of the lung, this region was not cross-tolerant to 1-nitronaphthalene in ozone-exposed animals. Injury to the central acinus by 1-nitronaphthalene was exacerbated significantly by prior long-term exposure to ozone.

Long-term exposure to ozone alters the lung both structurally and biochemically. In rodents, long-term exposure to ozone results in reorganization of the central acinus, the region of transition between the conducting airways and the alveolar gas exchange region. The resultant bronchiolarization of the alveolar duct is believed to be a key factor in the development of the tolerance to oxidant stress observed after long-term exposure to ozone. Metabolic changes resulting from ozone exposure include elevations in a number of antioxidant enzymes (Plopper et al., 1994) and glutathione (Duan et al., 1996). Also modified by ozone exposure are the cytochrome P450 monooxygenases, although data on P450 activity after ozone exposure have been difficult to interpret, in part due to methods inadequate to characterize local changes in metabolic potential. The key issue is whether the changes associated with long-term ozone exposure render the lung more or less susceptible to other environmental contaminants acting via different mechanisms. Cross-tolerance and how exposure to one toxicant influences the response to another are critical issues that have not been fully addressed.

This study demonstrates that tolerance to ozone rendered a primary target for oxidant pollutant gases, the central acinar epithelium, more susceptible to toxicity by a ubiquitous bioactivated environmental contaminant. The dose-response shifted making ciliated cells in the central acinus of ozone-exposed animals more sensitive to 1-nitronaphthalene toxicity than those in filtered air-exposed animals. The response to 1-nitronaphthalene in intrapulmonary airways proved more difficult to sample given the heterogeneity of response within the intrapulmonary airway tree, but did not appear to differ between filtered air- and ozone-exposed animals. Given these factors, no attempts were made to quantify this response. The trachea, a site of low P450 activity (Watt et al., 1999) and low rates of 1-nitronaphthalene metabolism, was the site of most severe 1-nitronaphthalene toxicity with no apparent differences between filtered air- and ozone-exposed animals. In the trachea, the critical question was not whether there was a quantifiable difference in response to 1-nitronaphthalene in filtered air- and ozone-exposed rats, but why a region with low P450 activity and low rates of 1-nitronaphthalene metabolism exhibited severe injury. A characteristic difference between the response of the trachea and the rest of the tracheobronchial tree was the infiltration of inflammatory cells into the trachea with high doses of 1-nitronaphthalene. The development of tolerance to prolonged ozone exposure involves down-regulation of neu-
trophic migration (Paige and Plopper, 1999). However, this adaptive response to long-term ozone exposure did not preclude neutrophil infiltration after acute injury by another compound, suggesting that the ability of the epithelium to recruit neutrophils remains intact throughout the ozone exposure. The role of neutrophils in 1-nitronaphthalene-induced injury to tracheal epithelium is not clear, but emphasizes the site-specificity of the biological response and the important role inflammatory cells may play in some sites and not others.

This study raises issues of both scientific and public health concern. Nonciliated (“Clara”) cells are a well characterized target of a number of bioactivated lung toxicants due to their relatively high P450 activity (Plopper, 1993). In contrast, ciliated cells possess little, if any, P450 activity and have been generally regarded as a nontarget cell type for bioactivated lung toxicants. In the case of 1-nitronaphthalene, however, this and previous studies (Johnson and Riley, 1984; Rasmussen et al., 1986; Sauer et al., 1995, 1997; Paige et al., 1997) report ciliated cell toxicity that has yet to be explained. In the present study, the key difference between the response of filtered air- and ozone-exposed rats to 1-nitronaphthalene was the heightened degree of ciliated cell injury in those exposed to ozone. Although ciliated cells are tolerant to further acute oxidant injury after long-term exposure to ozone, and ciliated cells possess little, if any, of the enzymes necessary for the bioactivation of 1-nitronaphthalene, it is this cell type whose susceptibility to 1-nitronaphthalene is heightened after long-term exposure to ozone. The mechanism of ciliated cell toxicity by P450-activated toxicants is not clear. Whether metabolites of 1-nitronaphthalene generated in the Clara cell are stable enough to enter neighboring ciliated cells by inter- or extracellular pathways is not known. The binding of critical cellular macromolecules by metabolites is proposed as a general mechanism for toxicity of bioactivated compounds, but it is not known whether there is a critical target macromolecular unique to ciliated cells that may explain the enhanced susceptibility to 1-nitronaphthalene after long-term ozone exposure.

This apparent paradox, tolerance to oxidant injury coincident with increased susceptibility to a bioactivated toxicant, has particular relevance to human populations living in polluted urban areas. Tolerance to one pollutant, associated with elevated levels of protective enzymes, does not confer resistance to other pollutants and may even render sites in the lung more susceptible. These studies were conducted in a rodent model, using high doses of a toxicant administered systemically. It is difficult to extrapolate data derived from these experiments to human exposures to low concentrations of airborne 1-nitronaphthalene. Nonetheless, these findings suggest that the metabolic changes associated with chronic oxidant stress, as encountered in many urban areas, may significantly elevate susceptibility to bioactivated copollutants, thereby posing a considerable risk to human health.

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References


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