

Formaldehyde  
DNA  
Toxicity  
Review

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Chapter 12

## Mechanisms of Formaldehyde Toxicity

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The discovery that exposure to formaldehyde vapor could induce nasal carcinomas in rodents with striking species differences and an extremely sharp dose response (1, 2) stimulated the development of a series of research projects aimed at understanding the mechanisms involved in formaldehyde toxicity (see also Chap. 11, this volume). This presentation will review various aspects of tissue exposure and response, using preliminary data from investigations designed to fill some of the gaps in our knowledge of the pathogenesis of formaldehyde-induced disease.

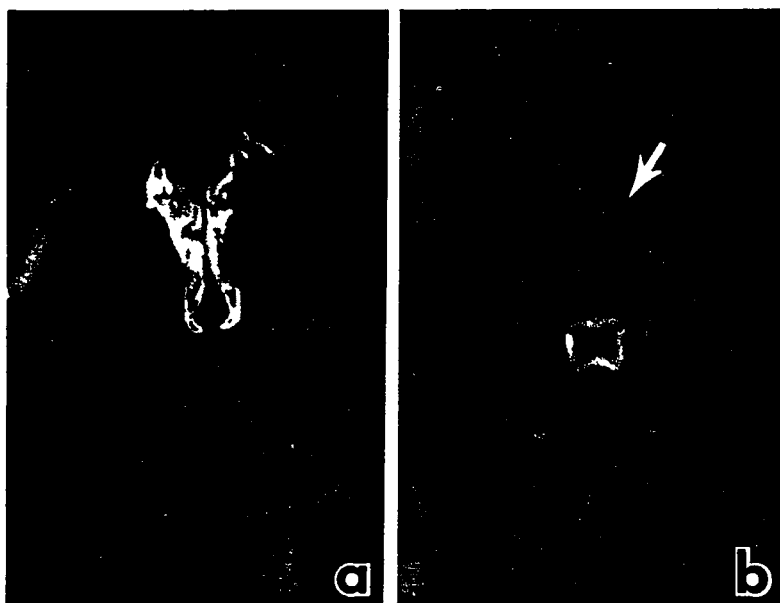
### **STUDIES ON THE DISTRIBUTION OF FORMALDEHYDE IN THE NASAL CAVITY**

Biochemical investigations on the absorption and distribution of [ $^{14}\text{C}$ ] formaldehyde ( $\text{CH}_2\text{O}$ ) have demonstrated that it is primarily deposited in the upper

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respiratory tract (see Chap. 4, this volume). In order to localize this deposition within the nasal cavity, naive or pretreated rats and mice were exposed to 15 ppm [ $^{14}\text{C}$ ] formaldehyde for 6 h. The animals were killed by decapitation immediately after removal from the chambers. The skin was removed from the heads, which were then frozen in carboxymethylcellulose for cryosectioning in an LKB PMV 2250. Autoradiographic films were prepared from transverse step sections of the nasal cavity using NS2T emulsion X-ray films (Eastman Kodak Co.) as previously described (3).

Formaldehyde-associated radioactivity was heavily deposited in the anterior nasal cavity of rats and mice. The localization of radioactivity correlated well with the distribution of lesions in similarly exposed animals, that is, activity was greatest in regions of respiratory epithelium over the maxilloturbinates and nasoturbinates and the lateral wall of the nasal cavity (Fig. 1a). An exception was noted for the ventral portion of the nasal cavity, which is lined with squamous epithelium. Radioactivity was heavily deposited in this area; however, minimal histologic evidence of toxicity was observed. This suggests that squamous epithelium is less sensitive to formaldehyde intoxication than is respiratory epithelium. The induction of squamous metaplasia as a response to  $\text{CH}_2\text{O}$  exposure and the relative resistance of squamous epithelium to toxicity suggest



**Figure 1** Autoradiograph of transverse sections of the nasal cavity from a rat exposed to 15 ppm [ $^{14}\text{C}$ ] formaldehyde for 6 h. Note the heavy deposition of radioactivity in the anterior portion (a) and the paucity of radioactivity in the region of olfactory epithelium (X) compared to moderate amounts of radioactivity in the nasopharynx of a posterior section (b) of nasal cavity.

that squamous metaplasia is a host defense mechanism to formaldehyde toxicity. A portion of the radioactivity located in the ventral squamous regions may be the result of mucociliary flow and gravity rather than direct exposure to formaldehyde vapor. Radioactivity may represent material covalently bound to mucus rather than reactive formaldehyde. The amount of radioactivity deposited in regions of olfactory mucosa in the nasal cavity was much less; thus radioactivity in posterior sections was primarily confined to the nasopharynx (Fig. 1*b*). Whole-body parasagittal sections of rats confirmed the anterior-posterior concentration gradient of [ $^{14}\text{C}$ ] formaldehyde but demonstrated the presence of radioactivity down to the level of the bronchial lining (Fig. 2). Bronchial radioactivity was similar to that of bone marrow and is thought to be the result of metabolic incorporations of the one-carbon pool. Minimal differences were apparent in formaldehyde distribution between naive rats and mice. When animals that had been exposed to 15 ppm of nonradioactive formaldehyde for 9 days prior to exposure to [ $^{14}\text{C}$ ] formaldehyde were compared to naive rats, a decrease in radioactivity in the dorsal olfactory epithelium of the anterior half of the nasal cavity and of the abdominal viscera was noted. Changes in airflow due to vascular congestion and inflammation may be responsible for decreases in nasal cavity deposition, while the decreased radioactivity associated with the abdominal viscera may reflect a decrease in mucociliary flow and subsequent swallowing of radioactive mucus. Sharp anterior-posterior concentration gradients, such as demonstrated in these investigations, might be expected for reactive chemicals with a high degree of water solubility.

### MORPHOLOGICAL STUDIES ON THE NASAL CAVITY

Since differences in airway volume, shape, and surface area could readily affect response patterns, we have undertaken a series of investigations on the normal

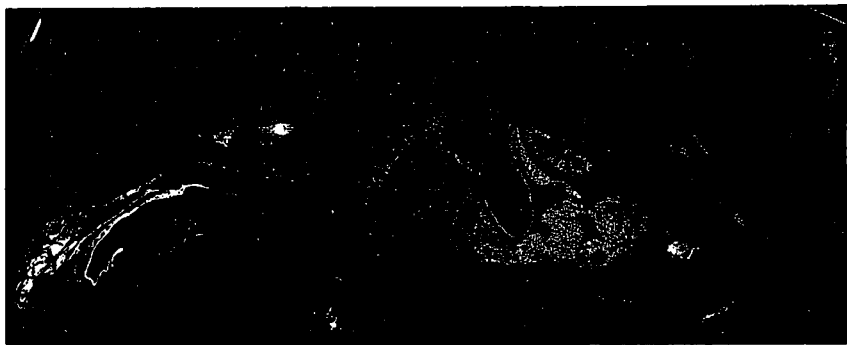


Figure 2 Parasagittal whole-body autoradiograph of a rat exposed to 15 ppm [ $^{14}\text{C}$ ] formaldehyde for 6 h. Note the heavy deposition of radioactivity in the nasal cavity and anterior half of the trachea, with additional moderate deposition in the bronchi of the lungs. Radioactivity in the abdominal viscera is probably the result of mucociliary clearance and metabolites.

structure of the rat and mouse nasal cavity using morphometric analysis. Conventional surface areas, volumes, and the distribution of the various epithelial types lining the nasal cavity in normal 7- and 16-week-old Fischer 344 male rats and B6C3F1 male mice have been mapped at the light microscopic level (4). Photographs of nasal transverse sections were analyzed using a Zeiss Videoplan computerized image analysis system programmed for measurement and evaluation of count, area, perimeter, and length. The results are shown in Table 1. The percentage of the surface area covered by the various epithelial types lining the nasal cavity was similar in all animals studied. Little change in volume or surface area was present between 7- and 16-week-old mice, whereas the volume and surface area of the rat nasal cavity increased 165 percent and 168 percent, respectively. Utilizing the autoradiographic data on patterns of formaldehyde deposition, the morphometry provides baseline data that can be used to help quantitate the "dose" of inhaled chemical reaching the nasal cavity and may be useful in understanding differences in species' response to the same concentration of inhaled chemical. For example, using minute volumes for rats and mice exposed to 15 ppm formaldehyde vapor (5; see also Chap. 3, this volume), the dose of formaldehyde available for absorption is 0.154 and 0.075  $\mu\text{g}/\text{min}/\text{cm}^2$  in rats and mice, respectively. Thus, the mouse nasal mucosa is exposed to only half the amount of formaldehyde that the rat nasal mucosa is exposed to. This dose correlates well with tumor data, in which the incidence of nasal carcinoma is similar in rats exposed to 6 ppm and mice exposed to 15 ppm of formaldehyde vapor (see Chap. 11, this volume). Morphometric analysis of the nasal cavity could also be used to quantitate changes in epithelial types (e.g., squamous metaplasia) that occur in subchronic and chronic inhalation studies. One must bear in mind, however, that surface areas determined by light microscopy are dramatically different from actual cellular surface areas when the epithelium is composed of cells with cilia and microvilli. Measurements derived by light microscopic morphometry do, however, closely approximate the surface area of the mucous blanket that normally lines the nasal cavity and provides the initial site for formaldehyde absorption.

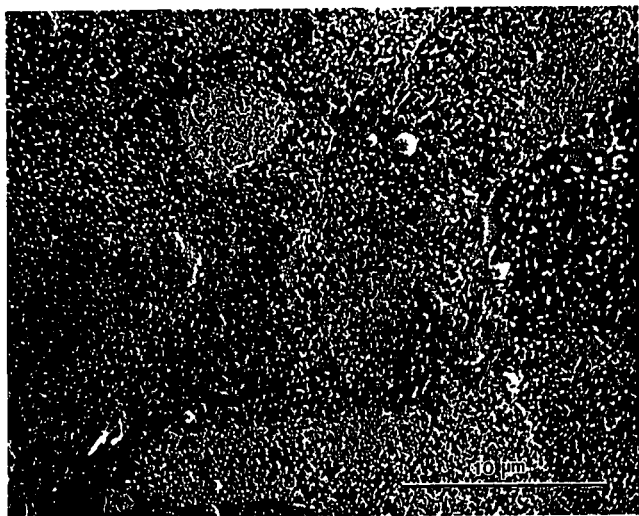
Preliminary transmission and scanning electron microscopic studies of the rat nasoturbinate have identified nine different cell types within the respiratory epithelium. Nasal epithelial cells become progressively taller from anterior to posterior. The anterior cells (behind the normal squamous epithelium) have few surface microvilli, while cells farther posterior have more numerous microvilli (Fig. 3). Columnar nonciliated epithelial cells having a large amount of smooth endoplasmic reticulum in the apical cytoplasm may represent more metabolically active cell types (Fig. 4). The percentage of cells having apical cilia increases from anterior to posterior (Fig. 5). Such cells are thought to play a major role in normal mucociliary clearance mechanisms and may represent a potential target for formaldehyde intoxication. Changes in blood flow and congestion are likely to cause alterations in airflow, which in turn could

**Table 1 Morphometric Analysis of the Rat and Mouse Nasal Cavity**

	Rat		Mouse	
	7 Wk (115 g)	16 Wk (288 g)	7 Wk (30 g)	16 Wk (33 g)
Length (mm)	7.3 ± 0.0*	9.1 ± 0.3	4.9 ± 0.7	5.1 ± 0.08
Volume (mm <sup>3</sup> )	155.5 ± 1.3	256.7 ± 4.1	32.5 ± 3.2	31.5 ± 2.1
Surface area (mm <sup>2</sup> )				
Squamous epithelium (mm <sup>2</sup> )	27.7 ± 1.9	44.2 ± 5.2	20.9 ± 0.4	20.6 ± 2.2
Respiratory epithelium	352.4 ± 4.9	623.1 ± 14.0	132.4 ± 5.7	133.9 ± 4.6
Olfactory epithelium	418.5 ± 19.2	675.2 ± 43.0	125.5 ± 4.0	136.9 ± 7.3
Total surface area	798.6 ± 20.2	1343.5 ± 55.0	277.7 ± 16.1	289.0 ± 13.1

*Note:* From Gross et al. (9).

\*Values are expressed as mean of 3 animals ± standard deviation.



**Figure 3** Scanning electron micrograph of anterior respiratory epithelial cells with microvilli.

alter the extent and site of toxicity. The extensive number of blood vessels and sinuses can be readily appreciated by examining perfused specimens with light or electron microscopy (Fig. 6).

### ACUTE TOXICITY FOLLOWING FORMALDEHYDE EXPOSURE

Acute cell degeneration, necrosis, and inflammation were evident in the nasal cavities of rats exposed to 15 ppm formaldehyde vapor for 1-9 days (6 h/day).



**Figure 4** Transmission electron micrograph of a columnar cell with considerable smooth endoplasmic reticulum.

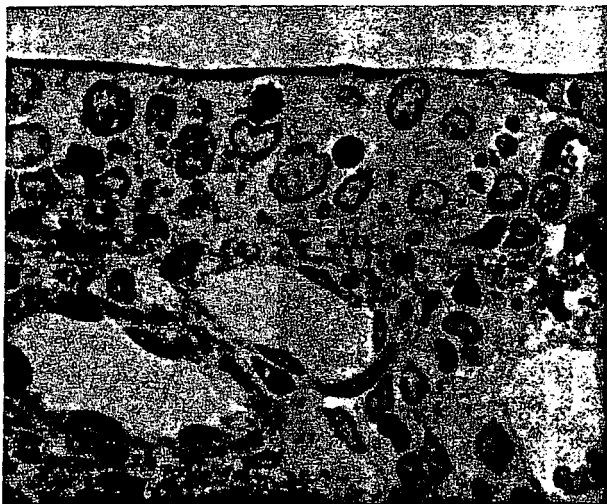


**Figure 5** Scanning electron micrograph of ciliated respiratory epithelial cells from the nasoturbinates.

Initial lesions were most severe on the tips of the maxilloturbinates and nasoturbinates. Acute degeneration of the respiratory epithelium, with edema and congestion, was evident at the end of 1 day's exposure (Fig. 7). This was followed by ulceration, necrosis, and an influx of inflammatory exudate at days 3-9 (Fig. 8). Early squamous metaplasia was detected over the nasoturbinates and maxilloturbinates, median septum, and lateral wall after as little as 5 days of formaldehyde exposure (Fig. 9). Examination of turbinates from rats exposed 5 days and allowed to recover for 48 h demonstrated considerable regeneration. Areas that were frequently ulcerated, such as the lateral wall, had single thin strap cells covering areas normally occupied by three or more cuboidal epithelial



**Figure 6** Scanning electron micrograph of a transverse section of the rat nasal cavity. Note the large number of blood vessels just under the epithelial surfaces.



**Figure 7** A 1  $\mu$ m plastic section of a perfused nasoturbinate from a rat exposed to 15 ppm formaldehyde for 6 h. Note the early degeneration and swelling. X 1375.

cells (Fig. 10). In contrast to these changes in the respiratory epithelium, mild serous rhinitis was the principal lesion in regions of olfactory epithelium. Mild degenerative and inflammatory changes were also evident in the nasopharynx.

The mouse was similar, but less severe than the rat, in its acute response to formaldehyde exposure. Five days' exposure to 15 ppm formaldehyde vapor caused degeneration, focal necrosis, and inflammation of the nasoturbinates



**Figure 8** Focal ulceration, epithelial hyperplasia, necrosis, and rhinitis of the nasoturbinate of a rat exposed to 15 ppm formaldehyde for 3 days (6 h/day). X 152.



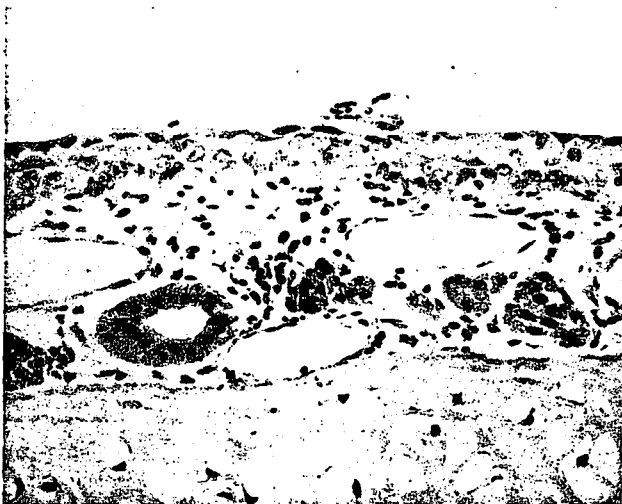


Figure 9 Early squamous metaplasia of the respiratory epithelium after 5 days' exposure to 15 ppm formaldehyde. X 304.

and maxilloturbinates and to the lateral walls, but there was minimal toxicity to areas lined by squamous or olfactory epithelium.

By comparing these acute toxicity studies with data from the 3-month exposures reported by Rusch (see Chap. 10, this volume) and the interim sacrifice data from the formaldehyde bioassay (see Chap. 11, this volume), it is clearly evident that adaptive changes occur. The extent and severity of formaldehyde-



Figure 10 A region of the lateral wall is covered by single "strap" cells following 5 days' exposure to 15 ppm (6 h/day) and 2 days recovery. X 608.

induced toxicity diminished with time. This may be due to changes in respiratory physiology, as well as to alterations at the cellular level, such as squamous metaplasia, epithelial hyperplasia, and increased detoxification pathways.

### EFFECTS OF FORMALDEHYDE EXPOSURE ON CELL TURNOVER

A prominent response to cell loss associated with toxicity is compensatory cell replication. Surviving cells undergo division in order to replace dead cells and to increase the thickness of the epithelium. Preliminary studies on the effect of 15 ppm of formaldehyde vapor, 6 h/day for 5 days, have been conducted in rats. One day prior to exposure the animals had an osmotic mini-pump containing a 7-day supply of  $^3\text{H}$ -thymidine implanted in the peritoneal cavity. Following the fifth day of exposure the animals were anesthetized with pentobarbital and killed by vascular perfusion with 10% neutral buffered Formalin; the heads were decalcified, embedded, and sectioned and slides were prepared for autoradiography. Control rats had 5/2686 (0.19 percent) labeled respiratory epithelial cells, while formaldehyde-exposed animals had 634/4712 (13.5 percent), which represents a 71-fold increase in cell replication. Sequential pulse labeling studies following 1, 3, 5, or 9 days of formaldehyde exposure demonstrated that maximum cell proliferation occurred after 3 days. A 10- to 20-fold increase in cell replication occurred when rats were exposed for 3 days to 6 or 15 ppm formaldehyde vapor (Fig. 11) and when mice were exposed to 15 ppm. Similar

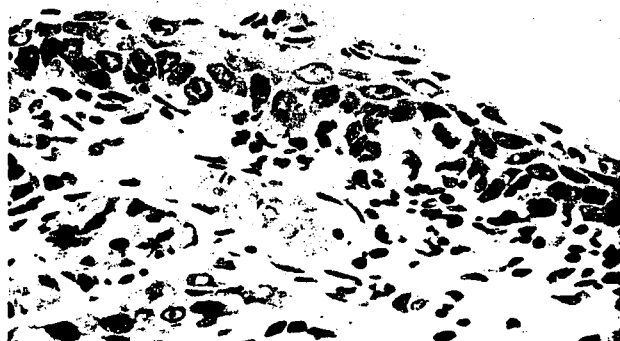


Figure 11 Light microscopic autoradiograph of the respiratory epithelium of a rat exposed to 6 ppm formaldehyde for 3 days. Note the large number of cells labeled with  $^3\text{H}$ -thymidine. X 608.

exposures of rats to 0.5 or 2.0 ppm and mice to 0.5, 2.0, or 6.0 ppm formaldehyde (Fig. 12) did not result in increased cell turnover in the nasal cavity.

### MACROMOLECULAR INTERACTIONS WITH FORMALDEHYDE

The initiating event in chemical carcinogenesis is thought to involve covalent binding of reactive compounds to specific sites on the DNA (6). Such damage can be enzymatically removed by cellular DNA repair systems. Furthermore, cell division is required prior to DNA repair for carcinogenesis to occur. In the case of formaldehyde, unwinding of the double helix during cell replication may also be required to expose critical sites on the DNA to covalent binding (7).  $\text{CH}_2\text{O}$  does not react with native double-stranded DNA, but it does react with denatured DNA (8). Denaturation destroys H-bonding between two strands of the molecule similar to the unwinding of DNA during replication. This phenomenon could explain the apparent cell-cycle specificity of  $\text{CH}_2\text{O}$ . Mutagenesis in *Drosophila* is restricted to the period of chromosome replication preceding meiosis (8). Exponentially growing cultures of yeast exhibit greater sensitivities to lethality and mutagenesis than do stationary cultures (9). Carcinogenesis in the rat nasal epithelium may be directly related to the increased cell division resulting from toxicity. During the increased cell division, the likelihood of interaction of  $\text{CH}_2\text{O}$  with DNA would increase, as would fixation of adducts before DNA repair could occur.

The reaction of  $\text{CH}_2\text{O}$  with macromolecules occurs largely by way of amino

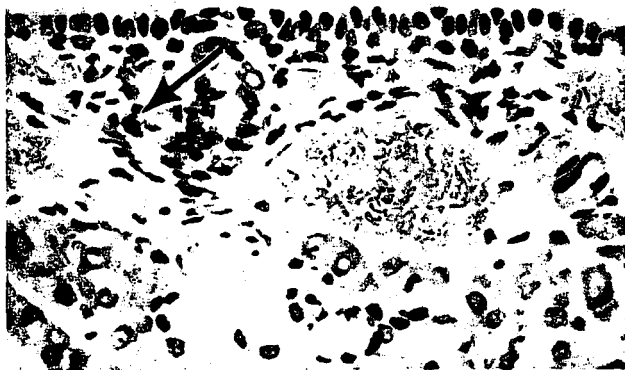
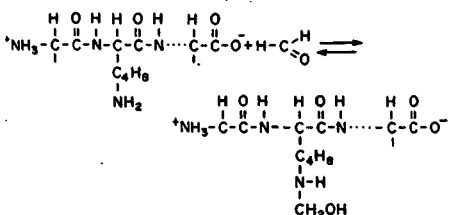
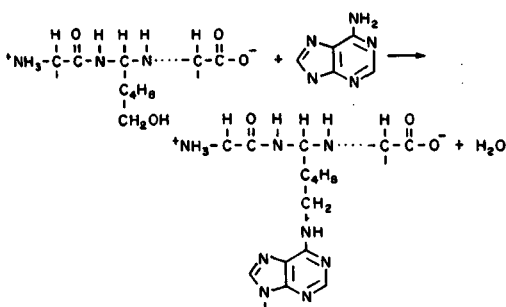


Figure 12 Light microscopic autoradiograph from a rat exposed to 2 ppm formaldehyde for 3 days. Note the lack of  $^3\text{H}$ -thymidine labeled epithelial cells. A labeled stromal cell is present in the submucosa (arrow). X 608.

## 1. Formation of Unstable Methylol Derivatives:



## 2. Formation of Stable Condensation Product (Methylene Bridge):

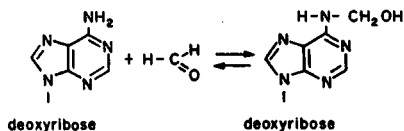


**Figure 13** Chemical reaction thought to be involved in protein-DNA cross-links due to formaldehyde.

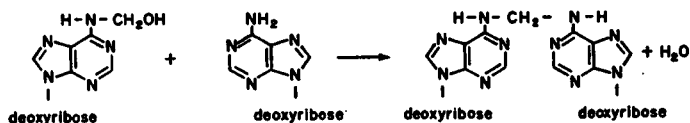
groups, such as those in proteins and nucleic acids. A two-step mechanism has been proposed (10), the first step of which is the fast, reversible formation of unstable methylol derivatives which may lose water to form a methylene Schiff base. The irreversible formation of a stable condensation product, a methylene cross-link, may occur by way of nucleophilic attack on the methylene carbon. These cross-links could occur between two proteins, between DNA and protein (Fig. 13), or between DNA and DNA (Fig. 14). By involvement of DNA, the latter two processes could constitute the mechanism by which an irreversible genetic change occurs. Biological implications of such reactions have been demonstrated by comparing DNA repair deficient and proficient strains of *Escherichia coli*, yeast, and mammalian cells (8, 11).

One of the most useful techniques for evaluating DNA-protein and DNA-DNA cross-links is alkaline elution (12, 13). This technique measures the amount of DNA retained on a filter versus the amount of DNA eluting through the filter (Fig. 15). Typically, about 90 percent of control DNA from tissues or cultured cells is retained on the filter. When single-strand breaks are present, the amount of DNA eluting increases proportional to the amount of damage.

## 1. Formation of Unstable Methylol Derivatives:



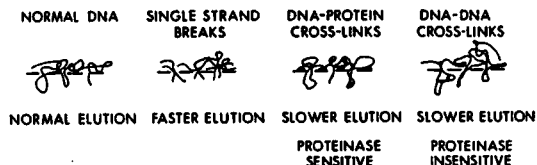
## 2. Formation of Stable Condensation Product (Dimer)



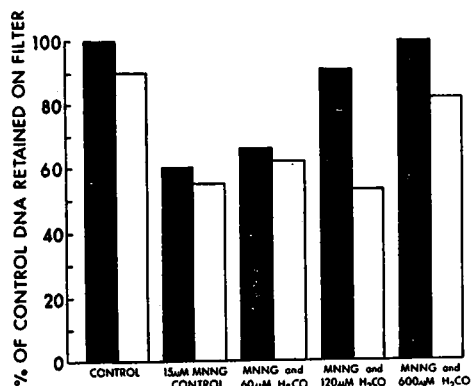
**Figure 14** Possible reactions involved in the formation of DNA-DNA dimers by formaldehyde.

If, however, protein-DNA or DNA-DNA cross-links exist, DNA elution is decreased. By treating the DNA with proteinase K, it is possible to distinguish between protein-DNA and DNA-DNA cross-links. We have utilized this method to examine the interactions of formaldehyde and DNA.

In order to increase the sensitivity of the assay for cross-linked DNA, single-strand breaks or alkali-labile sites were induced in control and treated samples. V79 cells were exposed to 0, 60, 120, or 600  $\mu$ mol of formaldehyde solution for 1 h followed by 15  $\mu$ mol of N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) for 15 min to induce a uniform number of single-strand breaks and alkali-labile sites in the DNA. DNA was eluted from the filters after lysing the cells in the presence or absence of proteinase K. A dose-dependent increase in retention of DNA on the filters was associated with formaldehyde exposure (Fig. 16). This was reversed by proteinase K, providing strong evidence for protein-DNA cross-links. Cells treated with 120  $\mu$ mol formaldehyde and allowed to grow for 24 h before exposure to MNNG did not show increased DNA retention on the filter, indicating that DNA repair processes had removed the cross-links. Recent studies



**Figure 15** Schematic on the effect of various forms of DNA damage on the alkaline elution assay.



**Figure 16** Effect of formaldehyde on the alkaline elution of MNNG-treated V79 cells in the presence (open bars) and absence (closed bars) of proteinase K.

by Ross and Shipley confirmed these findings in L1210 cells and demonstrated that DNA-protein cross-links occur at nonlethal concentrations of formaldehyde (14, 15). Similar results have been reported for yeast (16).

Reaction between  $\text{CH}_2\text{O}$  and DNA has been shown to occur with bases, nucleotides, nucleosides, synthetic polynucleotides, and intact DNA. Using high performance liquid chromatography, cross-linked nucleosides were isolated and identified from formaldehyde-treated DNA (17). Methylene-bridged products included dCyd- $\text{CH}_2$ -dGuo, dGuo- $\text{CH}_2$ -dGuo, dGuo- $\text{CH}_2$ -dCyd, dGuo- $\text{CH}_2$ -dAdo, and dAdo- $\text{CH}_2$ -dAdo. The relative amounts and biological significance of these DNA-DNA cross-links remain to be determined, however, since they were only demonstrated after reacting formaldehyde and calf thymus DNA for 40 days. Although the products of chemical reactions between  $\text{CH}_2\text{O}$  and DNA bases have been isolated and characterized, no such reaction product has been isolated from formaldehyde-treated cells or tissues.

## DISCUSSION

It should be obvious from the data presented above, and elsewhere in this volume, that mechanisms responsible for formaldehyde carcinogenesis are complex. Formaldehyde-induced squamous cell carcinomas of the nasal cavity exhibit an extremely sharp dose-response curve and prominent species differences. Understanding the pathogenesis of these differences is crucial for proper risk assessment. While a great deal of additional research is necessary, it is possible to begin piecing together some of the prominent mechanisms on which the outcome depends. First, it is clear that areas of contact, deposition, and toxicity are similar in rats and mice. These endpoints are dependent on the species' respiratory physiology and response to acute versus chronic exposure. Using such data it is possible to calculate the dose received by the target organ.

By incorporating this information into the bioassay data, the major species difference in dose response disappears, since mice and rats receiving a similar dose developed a similar low incidence of squamous cell carcinomas. Furthermore, similar increases in cell replication were induced by exposure of rats to 6 ppm and mice to 15 ppm formaldehyde. Since cell replication can be a compensatory response to toxicity and may have profound effects on the availability of covalent binding sites on the DNA, toxic exposure levels may greatly enhance covalent binding. Since protein-DNA cross-links represent the major DNA adduct and they can be rapidly repaired, increased cell proliferation may also be important in fixing the mutational events thought to be responsible for initiation. Nothing is presently known about formaldehyde as a promoter; however, increases in cell turnover may accelerate the process of carcinogenesis. The fact that only exposure concentrations associated with squamous cell carcinoma in rats and mice resulted in increased cell proliferation lends strong support to the hypothesis that increased cell proliferation is a critical event in formaldehyde carcinogenesis.

A separate but related consideration is the relative importance of concentration versus cumulative dose. Cytotoxicity and increased cell proliferation appear to be related to the former. If one compares the cumulative dose to rats exposed to 15 ppm formaldehyde 6 h/day, 5 days/wk (450 ppm-h/wk) with that of rats exposed to 3 ppm for 22 h/day, 7 days/wk (462 ppm-h/wk) it is readily apparent that similar cumulative doses of formaldehyde resulted, yet the lesions (see Chaps. 10 and 11, this volume) and, presumably, the amount of cell proliferation are vastly different. It would appear then that formaldehyde concentration is the most important consideration in determining response and that the response changes drastically when toxic concentrations are achieved. Additional research is needed to better define the concentration-response relationships associated with formaldehyde exposure, as these data will be crucial for cogent risk assessment.

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# FORMALDEHYDE TOXICITY

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Mechanisms of Formaldehyde Toxicity

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The discovery that exposure to formaldehyde vapor could induce nasal carcinomas in rodents with striking species differences and an extremely sharp dose response stimulated the development of a series of research projects aimed at understanding the mechanisms involved in formaldehyde toxicity. This presentation will review various aspects of tissue exposure and response, using preliminary data from investigations designed to fill some of the gaps in our knowledge of the pathogenesis of formaldehyde induced disease.