Relevance of Particle-induced Rat Lung Tumors for Assessing Lung Carcinogenic Hazard and Human Lung Cancer Risk

Joe L. Mauderly

Lovelace Respiratory Research Institute, Albuquerque, New Mexico

Rats and other rodents are exposed by inhalation to identify agents that might present hazards for lung cancer in humans exposed by inhalation. In some cases, the results are used in attempts to develop quantitative estimates of human lung cancer risk. This report reviews evidence for the usefulness of the rat for evaluation of lung cancer hazards from inhaled particles. With the exception of nickel sulfate, particulate agents thought to be human lung carcinogens cause lung tumors in rats exposed by inhalation. The rat is more sensitive to carcinogenesis from nonfibrous particles than mice or Syrian hamsters, which have both produced false negatives. However, rats differ from mice and nonhuman primates in both the pattern of particle retention in the lung and alveolar epithelial hyperplastic responses to chronic particle exposure. Present evidence warrants caution in extrapolation from the lung tumor response of rats to inhaled particles to human lung cancer hazard, and there is considerable uncertainty in estimating unit risks for humans from rat data. It seems appropriate to continue using rats in inhalation carcinogenesis assays of inhaled particles, but the upper limit of exposure concentrations must be set carefully to avoid false-positive results. A positive finding in both rats and mice would give greater confidence that an agent presents a carcinogenic hazard to man, and both rats and mice should be used if the agent is a gas or vapor. There is little justification for including Syrian hamsters in assays of the intrapulmonary carcinogenicity of inhaled agents. — Environ Health Perspect 105(Suppl 5):1337–1346 (1997)

Key words: cancer, lung, inhalation, rat, mouse, hamster, particles, pollution, fibers

Introduction

In the absence of adequate information from humans, the potential carcinogenic hazards of agents encountered in the home, workplace, and general environment are often estimated from results of studies using animals. Moreover, data from animal carcinogenicity bioassays are sometimes used to develop quantitative estimates of human cancer risk per unit of exposure. Several interpretive challenges are encountered in using data from inhalation bioassays in rodents to estimate either the hazard or risk for induction of lung cancer in humans exposed to agents by inhalation. Not only does the carcinogenicity of an agent often vary among animal species, but the degree to which the response of any animal species represents potential human lung responses is often uncertain. For inhaled particles, increasing evidence shows that the proliferative and neoplastic responses of the rat lung to heavy, chronic exposures may not serve as good models for lung responses of humans to lesser exposures (1,2). The frequent use of the rat in cancer research and carcinogenesis bioassays, and the impact of the results on product development and exposure standards, make this a significant scientific and economic issue.

This paper reviews the contemporary evidence for the relevance of the rat lung tumor response to inhaled particles for estimations of human lung cancer hazard and risk. There are no data allowing direct comparisons of the responses of rat and human lungs to carcinogenic particles under identical, well-characterized exposure conditions in both species. Therefore, this review takes an indirect, three-step approach to the comparison. First, the evidence for carcinogenicity of inhaled agents in rats and humans is reviewed. Throughout this paper, the evidence for human lung cancer is drawn from the evaluations of the International Agency for Research on Cancer (IARC), as presented in its 1987 review (3) and updated in subsequent monographs. Second, the lung tumor responses of rats to inhaled agents are compared to those of mice and Syrian golden hamsters to review the interspecies similarities and differences that contribute to our present interpretive difficulties. These comparisons also include nonparticulate agents, to portray the full range of our present information on the usefulness of these species in inhalation carcinogenesis bioassays. Third, differences in the patterns of intrapulmonary particle retention and accompanying epithelial proliferative responses between rats and both mice and nonhuman primates are reviewed.

There are three limitations regarding the scope of this review. First, it focuses solely on intrapulmonary cancer, because intrapulmonary tumors of epithelial origin in rats exposed to particles give rise to the interpretive uncertainties of broadest current concern. Although mesothelioma and neoplasia in extrapulmonary airways also present important interpretive challenges, this review does not address those responses, except for the data in Table 1. Second, the listing of evidence (Tables 2–5) for the carcinogenicities of agents as positive (+), limited (±), or negative (−) should not be interpreted or referenced as an authoritative determination of carcinogenicity. No attempt was made to review all cited findings in sufficient detail to reconcile differences in terminology or to apply uniform criteria of statistical significance. These nonquantitative designations are solely the author’s and are presented to illustrate interspecies similarities and differences. The limited (±) symbol is used for responses that may have been significant in one study, but not in another; for responses in genetically sensitive strains but not in other strains; for responses in studies inadequate for statistical evaluation; or for responses in studies inadequately described. In no case, however, was the response of

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Address correspondence to Dr. J.L. Mauderly, Lovelace Respiratory Research Institute, 2425 Ridgecrest SE, Albuquerque, NM 87108. Telephone: (505) 262-7938. Fax: (505) 262-7043. E-mail: jmauderl@lri.org

Abbreviations used: IARC, International Agency for Research on Cancer; NTP, U.S. National Toxicology Program.
Table 1. Evidence of carcinogenicity in animals for agents determined by IARC to have sufficient or limited evidence of carcinogenicity in humans.\(^a\)

| Evidence from humans | Evidence from animals\(^b\) |
|----------------------|-----------------------------|
|                      | No | S | L | I | ESL | ND |
| All organs, by all routes of exposure | 38 | 25 | 8 | 4 | 0 | 1\(^c\) |
| Sufficient | 18 | 14 | 2 | 2 | 0 | 0 |
| Limited | 56 | 39 | 10 | 6 | 0 | 1 |
| Respiratory tract, by inhalation exposure | 15 | 11 | 1 | 1 | 1\(^d\) | 1\(^e\) |
| Sufficient | 5 | 4 | 1 | 0 | 0 | 0 |
| Limited | 20 | 15 | 2 | 1 | 1 | 1 |

Abbreviations: ESL, evidence suggesting lack; I, inadequate; L, limited; ND, no data; S, sufficient. \(^a\)Agents or families of agents listed by IARC, excluding occupations associated with carcinogenicity. \(^b\)Information from IARC monographs, updated in some cases to include results from more recent animal studies. \(^c\)No data from animals exposed to treosulphan by any route. \(^d\)Inhalation bioassays of nickel sulfate were negative in rats and mice. \(^e\)No data from animals exposed to arsenic compounds by inhalation.

Table 2. Nonfibrous particles causing intrapulmonary lung tumors in rodents exposed by inhalation.

| Nonfibrous particles | Rat | Mouse | Hamster | IARC\(^d\) | Reference |
|----------------------|-----|-------|---------|------------|-----------|
| Alpha-emit particle radionuclides | + | + | + | X | (16-19) |
| Antimony ore | + | ND | ND | X | (20) |
| Antimony trioxide | + | ND | ND | 2B | (20) |
| Beryllium fluoride | + | ND | ND | 1\(^f\) | (21,22) |
| Beryllium hydrogen phosphate | + | ND | ND | 1\(^f\) | (22,23) |
| Beryllium metal | + | + | ND | 1\(^f\) | (22,24) |
| Beryllium sulfate | + | ND | ND | 1\(^f\) | (13,22) |
| Beryll ore | + | ND | ND | X | (26) |
| Beta-emit particle radionuclides | + | + | + | X | (26-26) |
| Cadmium chloride | + | + | + | 1\(^f\) | (22,29,30) |
| Cadmium oxide | + | + | + | 1\(^f\) | (22,29,30) |
| Cadmium sulfate | + | + | + | 1\(^f\) | (22,29,30) |
| Cadmium sulfide | + | + | + | 1\(^f\) | (22,29,30) |
| Calcium chromate | + | + | ND | 3\(^f\) | (8,31,22) |
| Chromium dioxide | + | ND | ND | 2B | (8,33) |
| Carbon black | + | ND | ND | 2B | (5,6,34) |
| Coal dust | + | ND | ND | X | (35) |
| Coal tar aerosol | + | + | ND | 1 | (3,36,37) |
| Nickel carbonyl | + | ND | ND | 1\(^f\) | (8,38) |
| Nickel metal | + | + | ND | 1\(^f\) | (8,39) |
| Nickel oxide | + | + | ND | 1\(^f\) | (8,10,16) |
| Nickel sulfide | + | + | ND | 1\(^f\) | (8,11) |
| Oil shale dust | + | ND | ND | X | (40,41) |
| Polymetric methylene diphenyl disocyanate | + | ND | ND | 3 | (3,42) |
| Silica (crystalline) | + | ND | ND | 2A | (43-45) |
| Solvent-refined coal solids | + | ND | ND | X | (48) |
| Talc (asbestos-free) | + | ND | ND | 3 | (3,16,47) |
| Titanium dioxide | + | ND | ND | X | (50) |
| Titanium tetrachloride (hydrolysis products) | + | ND | ND | X | (51) |
| Volcanic ash | + | ND | ND | X | (51) |
| Zinc manganese beryllium sulfate | + | ND | ND | X | (23) |

Abbreviations: +, limited; +, positive; -, negative; X, not classified by IARC. \(^d\)IARC classification for human carcinogenesis, regardless of target organ or exposure route. \(^e\)IARC classification for family of compounds rather than individual compound.

In rats considered either positive or limited if the only reported tumors were the lesions termed "squamous cyst" (4,5), "benign keratinizing cystic squamous cell tumor" (6), or "proliferative keratin cyst" (7) without mention of accompanying adenomas or carcinomas. Despite differences in terminology, it is generally agreed that these lesions are rarely, if ever, seen in other species and have no parallel in human lung responses (7). Third, with the exception of the information listed in Table 1, "All Organs, by All Routes of Exposure," this review is limited to the results of inhalation exposures. To provide results directly comparable to those from humans exposed by inhalation, intratracheal instillation or intrapulmonary implantation dosing was not considered in this review.

Carcinogenicity of Inhaled Agents in Rat versus Human Lungs

It is useful to begin by reviewing the overall evidence for carcinogenicity in animals for agents thought to be carcinogens in humans (Table 1). A review of IARC monographs and supplements to date (September 1996) reveals 56 agents listed as having sufficient or limited evidence of carcinogenicity in any organ of humans exposed by any route (Table 1). Of these 56 agents, there is sufficient or limited evidence of carcinogenicity in any animal species exposed by any route for 49 agents. IARC reports inadequate evidence in animals for six agents, and that one known human carcinogen, treosulphan, has not been tested in animals. The point of this comparison is that all known or strongly suspected human carcinogens that have been tested in animals are carcinogenic in at least one mammalian animal species by some route of exposure.

IARC lists 20 agents having sufficient or limited evidence of carcinogenicity in the respiratory tract of humans exposed by inhalation (Table 1, "Respiratory Tract, by Inhalation Exposure"). These agents include those causing nasal, extrapulmonary airway, and mesothelial cancer as well as intrapulmonary cancer. Of these 20, there is sufficient or limited evidence of respiratory tract carcinogenicity in animals exposed by inhalation for 17 agents, and some, but inadequate, evidence for one agent. Arsenic compounds, while carcinogenic by intratracheal instillation and other routes of exposure, have not been tested in animals by inhalation. Therefore, with the possible exception of arsenic compounds and nickel sulfate (discussed below), there is no known or strongly suspected inhaled human respiratory tract carcinogen that is not also a respiratory tract carcinogen in at least one animal species exposed by inhalation.

Nickel sulfate was specified by IARC as a known lung carcinogen in humans exposed by inhalation (8); however, nickel sulfate hexahydrate was not carcinogenic in rats or mice exposed chronically by inhalation in a U.S. National Toxicology Program (NTP) bioassay (9). This finding is significant because it is the only known case of a declared human lung carcinogen...
Table 3. Fibers causing intrapulmonary lung tumors in rodents exposed by inhalation.

| Fiber                        | Rat | Mouse | Hamster | IARC | Reference |
|------------------------------|-----|-------|---------|------|-----------|
| Aramid                       | +   | ND    | ND      | X    | (53)      |
| Asbestos, amosite            | +   | −     | ND      | 1b   | (54,55)   |
| Asbestos, anthophyllite      | +   | ND    | ND      | 1b   | (55)      |
| Asbestos, chrysotile         | +   | ±     | ±       | 1b   | (54–56)   |
| Asbestos, crocidolite        | +   | −     | ND      | 2b   | (54,55,59) |
| Ceramic, kaolin              | +   | ND    | ND      | 2b   | (57,58,60,61) |
| Ceramic, alumina zirconia silica | +   | ND    | ND      | 2b   | (57,60)   |
| Potassium octatitanate       | ±   | ND    | ND      | X    | (62)      |
| Rockwool                     | ±   | ND    | ND      | 2B   | (60,63)   |

*IARC classification for human carcinogenesis regardless of target organ or exposure route. 

Table 4. Complex mixtures and combinations of agents causing intrapulmonary lung tumors in rodents exposed by inhalation.

| Mixtures and agents                | Rat | Mouse | Hamster | IARC | Reference |
|-----------------------------------|-----|-------|---------|------|-----------|
| Artificial smog [ozonized gasoline vapor] | ND  | +     | ND      | X    | (64,65)   |
| Benzene| pyrene + sulfur dioxide (SO₂) | +   | ND    | −     | 2A   | (3,12,66) |
| Cadmium oxide + zinc oxide        | +   | ND    | ND      | 1p   | (22,67)   |
| Coal smoke                        | +   | +     | ND      | X    | (68)      |
| Coal tar pitch + CB               | +   | ND    | ND      | 1    | (3,37)    |
| Coal tar pitch + CB + SO₂ + NO₂ + HCO | +   | ND    | ND      | 1    | (3,37)    |
| Diesel exhaust                    | ±   | +     | −       | 2A   | (5,6,68,70) |
| Plutonium-239 dioxide + beryllium metal | +   | ND    | ND      | 1    | (22,71)   |
| Plutonium-239 dioxide + tobacco smoke | +   | ND    | ND      | 1    | (3,72)    |
| Radon + diesel exhaust            | +   | ND    | ND      | 1    | (60,73)   |
| Radon + ozone                     | +   | ND    | ND      | 1    | (60,74)   |
| Radon + tobacco smoke             | +   | ND    | ND      | 1    | (60,73)   |
| Radon + uranium ore dust          | ND  | +     | ND      | 1    | (60,75)   |
| Tobacco smoke                     | ±   | −     | −       | 1    | (3,16,72) |
| Wood smoke                        | +   | +     | ND      | X    | (68)      |

CB, carbon black. *IARC classification for human carcinogenesis regardless of target organ or exposure route. 

Table 5. Gases and vapors that cause intrapulmonary lung tumors in rodents exposed by inhalation.

| Gases and vapors                  | Rat | Mouse | Hamster | IARC | Reference |
|-----------------------------------|-----|-------|---------|------|-----------|
| Benzene                           | ND  | +     | ND      | 1    | (3,76,77) |
| Bis[chloromethyl]ether            | +   | +     | ±       | 1    | (3,13)    |
| 1,3-Butadiene                     | −   | +     | ND      | 2B   | (3,78,79) |
| Bromoethane (ethyl bromide)       | −   | +     | ND      | 3    | (80,81)   |
| Chloroethane (ethyl chloride)     | −   | +     | ND      | 3    | (81,82)   |
| Chloromethyl methyl ether         | ±   | ±     | ±       | 1    | (83,84)   |
| Diazomethane                      | ±   | ±     | ND      | 3    | (3,13)    |
| 1,2-Dibromoethane (ethylene dibromide) | +   | +     | ND      | 2A   | (3,85)    |
| 1,2-Dibromo-3-chloropropane       | +   | −     | ND      | 2B   | (3,13,86) |
| Dichloromethane (methylene chloride) | +   | −     | −       | 2B   | (3,87)    |
| 1,3-Dichloropropene              | +   | −     | ND      | 2B   | (3,88)    |
| 1,2-Epoxybutane                   | +   | −     | ND      | 2B   | (3,14)    |
| Ethylene oxide                    | −   | +     | ND      | 2A   | (3,78,89) |
| Hydrazine                         | ND  | +     | ND      | 2B   | (3,90)    |
| Mustard gas                       | ND  | +     | ND      | 1    | (3)       |
| Nitrogen                          | −   | +     | ND      | 2B   | (3,91)    |
| 3-Nitro-3-hexene                  | +   | +     | ND      | X    | (13)      |
| Ozone                             | −   | ±     | ND      | X    | (92)      |
| Tetrachloroethane                 | +   | −     | ND      | 2B   | (3,92)    |
| Trichloroethylene                 | −   | −     | −       | 3    | (94)      |
| Urethane                          | ND  | +     | ND      | 2B   | (3,85)    |
| Vinyl chloride                    | +   | +     | −       | 1    | (3,13,95) |
| Vinylidene chloride               | −   | +     | ND      | 3    | (3,96)    |
| Radon                             | +   | ND    | +       | 1    | (60,73,75) |

*IARC classification for human carcinogenesis regardless of target organ or exposure route.

Table 6 summarizes the current evidence from rats and other animals for the intrapulmonary carcinogenicity of the 13 inhaled particulate agents listed by IARC as having sufficient or limited evidence for lung carcinogenicity in humans exposed by inhalation. This list includes both agents comprised solely of particles and agents such as cigarette smoke and diesel exhaust that are mixtures in which some or all of the carcinogenic activity is thought to be associated with particles. Of these 13 agents, 11 have been evaluated in rats in inhalation bioassays adequate to produce useful results; arsenic compounds have not been evaluated by inhalation in rats, and there has been no adequate test of inhaled wood dust in rats. For inhaled particles other than nickel sulfate (as described above), the results from adequate studies in rats closely parallel those from humans.

Several agents listed in Table 6 reveal differences between the lung tumor responses of rats and those of other species. The literature citations for these agents are contained in Tables 2 to 5. There are six inhaled particulate agents for which the lung tumor response of mice is clearly less than that of rats: beryllium compounds, cadmium compounds, nickel oxide, tobacco smoke, asbestos, and diesel exhaust. There are two agents carcinogenic in rats that are negative in mice: nickel subsulfide and crystalline silica. The lung tumor response of hamsters is negative or less than that of rats for several agents positive in rats. Indeed, there is no particulate agent for which there is more than limited evidence of carcinogenicity in the lungs of hamsters exposed by inhalation. These comparisons show that there are differences among the lung tumor responses of rodents exposed by inhalation to agents known or strongly suspected of causing human lung cancer by inhalation exposure.

Carcinogenicity of Inhaled Agents in Rat versus Other Animal Lungs

This section reviews the available literature by which the intrapulmonary carcinogenicity...
Table 6. Evidence of intrapulmonary carcinogenicity in animals for inhaled particles determined by IARC to have sufficient or limited evidence for lung cancer in humans exposed by inhalation.

| Inhaled particles       | Rat   | Mouse | Other          |
|-------------------------|-------|-------|----------------|
| Sufficient evidence for human lung cancer |       |       |                |
| Arsenic compounds       | ND    | ND    | ND             |
| Beryllium compounds     | S*    | L*    | ESL, hamster   |
| Cadmium compounds       | S     | S     | ND             |
| Coal tar                | S     | ND    |                |
| Chromium VI compounds   | S     | S     | ND             |
| Nickel sulfate          | ESL   | ESL   | ND             |
| Mixed nickel oxides and sulfides | S*    | L*    | ND             |
| Tobacco smoke           | S     | L     | L, hamster, dog |
| Wood dust               | L*    | ND    | l, hamster     |
| Limited evidence for human lung cancer |       |       |                |
| Asbestos                | S     | L     | L, hamster     |
| Diesel exhaust          | S     | ND    | ESL, hamster   |
| Rockwool and slagwool   | L     | ND    | ESL, hamster   |
| Silica (crystalline)    | S     | ESL   | ND             |

Hamster, Syrian golden hamster. *Information from IARC monographs updated in some cases to include results from more recent animal studies. **Rats and mice exposed to nickel oxide or nickel sulfide separately rather than as a mixture. Nickel oxide positive in female but not male mice. Nickel sulfide negative in male and female mice.

of inhaled agents in rats, mice, and hamsters can be compared. This section builds on and updates earlier reviews by Laskin and Sellakumar in 1974 (12), Pepelko in 1984 (13), IARC in 1987 (3), Huff et al. in 1991 (14), and Hahn in 1995 (15). The following listings should not be construed as a thorough analysis of the existing data or of the potential carcinogenicity of any agent in humans. The listings are intended only to summarize our present understanding of interspecies differences in response, and to provide a source of key references for those wishing to evaluate the information in greater detail. The overall IARC evaluation of the agents, when available, is given in the tables as an aid to readers seeking literature on human responses; however, unlike the animal results, the evaluations for humans are not exclusively based on lung responses or exposure by inhalation. Finally, there is no attempt to list all agents to which animals have been exposed. Only those agents causing lung tumors in one or more species are listed. For negative studies, the reader is directed to the reviews by Pepelko (13) and Huff et al. (14), which include inhalation exposures regardless of outcome.

Nonfibrous particulate agents that cause lung tumors in rats, mice, or hamsters exposed by inhalation are listed in Table 2. These include 31 simple agents (e.g., beryllium metal), complex agents (e.g., coal tar), and families of agents (e.g., α- and β-emitting particulate radionuclides). All 31 agents were tested in rats exposed by inhalation and were either positive (29 agents) or produced limited evidence of carcinogenicity (2 agents) in that species. Coal dust is especially interesting because of its potential utility in comparing lung responses of rats and humans (4). There is extensive information on exposures of coal workers, amounts of coal dust retained in lungs, and pathogenicity of coal dust in producing coal workers’ pneumoconiosis and progressive massive fibrosis (1). There is a consensus that although coal dust can cause debilitating and fatal lung disease in humans, it does not cause lung cancer in humans (52). There has been no thorough dose response, long-term carcinogenicity bioassay of inhaled coal dust in rats. Martin et al. (35) exposed female Sprague-Dawley rats 5 hr/day, 5 days/week, on alternate weeks for 24 months to unspecified coal dust at 200 mg/m³ and reported lung tumors in 4 of 36 exposed rats and none in controls. While this study design provided only limited evidence, if an adequate bioassay found coal dust to be a lung carcinogen in rats, it would clearly be a false positive for predicting lung cancer hazard for humans.

Sixteen of the nonfibrous particulate agents were tested in mice, of which only five were clearly positive in that species (α-emitting radionuclides, β-emitting radionuclides, cadmium oxide, calcium chromate, and coal tar). Beryllium metal gave limited evidence by producing a slight increase in the incidence and multiplicity of lung adenomas in strain A/J mice, but a negative response in C3H/HeJ mice (24). Nickel oxide gave limited evidence by producing some evidence of carcinogenicity in the lungs of female, but not male, mice (10). Nine of these agents were positive in rats and negative in mice, including cadmium and nickel compounds thought to be lung carcinogens in humans. The cadmium and nickel results suggest that mice have given false negatives for human lung cancer prediction.

Only nine of the nonfibrous particulate agents were tested in hamsters, and the only positive response was some limited evidence of lung carcinogenesis for α-emitting radionuclides. The negative results in hamsters included two agents, β-emitting radionuclides and cadmium oxide, that were positive in both rats and mice. These findings reflect the low sensitivity of the hamster lung to carcinogenesis from inhaled particles in comparison to both the other rodents and humans.

Nine fibrous particles that caused lung tumors in rodents exposed by inhalation are listed in Table 3. These include four forms of asbestos, four man-made mineral fibers, and a synthetic organic fiber. All caused lung tumors in rats, although rockwool and potassium octatitanate were only weakly positive. Only three fibers, all asbestos, were tested in mice, and only chrysotile produced limited evidence of a positive response. Only two fibers were tested in hamsters. There is limited evidence of a positive response of the hamster to chrysotile asbestos, but kaolin-based ceramic fiber response was negative. The few comparisons available, therefore, suggest that the mouse and hamster are less sensitive than the rat to the induction of lung tumors by inhaled fibers, just as they are for nonfibrous particles.

Fifteen complex mixtures or combinations of agents reported to cause lung tumors in rodents are listed in Table 4. Of these mixtures, 13 contained particles and 2 (radon + ozone and "artificial smog" [ozonized gasoline vapor]) did not. All 13 mixtures tested in rats were positive in that species. Rats were not exposed to artificial smog or radon + uranium ore dust. Mice were exposed to five of the mixtures. Artificial smog, coal smoke, and wood smoke were positive in mice. Diesel exhaust caused increased incidences of lung tumors in Strain A and Sencar mice, but not in CD-1, NMRI, or C57BL/6N mice (6,70). Mixed results were observed in mice exposed chronically to cigarette smoke, with lung tumor incidences slightly increased in some studies and not in others (3). The equivocal responses of mice to diesel exhaust and tobacco smoke contrast with the clear response of the rat in multiple
studies of diesel exhaust (5,6,70) and the dose-related increase in lung tumor incidence recently observed in rats exposed chronically to cigarette smoke (72). Hamsters were exposed to three mixtures containing particles and chemical carcinogens (benzo(a)pyrene + sulfur dioxide, diesel exhaust, and tobacco smoke), and all of those studies were negative.

Twenty-four gases and vapors reported to cause lung tumors in rodents are listed in Table 5. Although these exposures did not include particles, the results are useful for comparison of responses among the species and evaluation of potential roles of the three species in inhalation carcinogenicity assays.

The differences between the responses of rats and mice to inhaled gases and vapors contrast with those for particles and mixtures. NTP chronic inhalation bioassays demonstrated that both 1,2-dibromo-3-chloropropane (86) and 1,3-epoxybutane (14) caused lung tumors in rats but not in mice. On the other hand, 11 compounds gave positive or limited evidence of carcinogenicity in mice but were negative in rats. Six compounds gave similar positive or limited results in both rats and mice. Only six gases or vapors were tested in hamsters, of which one was positive (radon), two produced limited responses (bis[chloromethyl]ether and chloromethyl methyl ether), and the others negative. There was no compound producing positive or limited responses in hamsters that was not also positive in one of the other species.

**Summary of Comparative Carcinogenicity Results**

The information in Tables 2 to 5 provides several important insights into the comparative lung carcinogenicity of inhaled agents in rats, mice, and hamsters, even though few of the comparisons involved identical exposures of the different species. First, it is clear that the rat is more sensitive than the mouse to lung carcinogenesis from inhaled particles. Nine nonfibrous particles were positive in rats and negative in mice, and two were positive in rats and gave only a limited response in mice. Two fibers were positive in rats and negative in mice, and one was positive in rats and gave a limited response in mice. Of the mixtures that contained particles, two were positive in rats while producing a limited response in mice. In the latter case, the limited response in mice occurred only in strains especially sensitive to carcinogenesis. None of the agents in these three classes were positive in mice and negative in rats.

Moreover, mice apparently yielded falsely negative results for several agents thought or known to be lung carcinogens in humans.

Second, it is clear that the hamster is less sensitive than either rats or mice to lung carcinogenesis from inhaled particles. Hamsters were exposed to 16 of the 56 agents listed in Tables 2 to 5, and only 3 agents caused limited or positive evidence of increased incidences of lung tumors. There is no known case of a positive result in hamsters for an agent negative in rats or mice. Thus, not only is the hamster of no apparent unique value in testing the lung cancer hazard of inhaled particles, but it can give falsely negative results for agents carcinogenic in humans.

Third, both rats and mice appear necessary for testing lung cancer hazards from inhaled gases and vapors. Two agents were positive in rats and negative in mice, and eleven were positive in mice and negative in rats. The hamster was not uniquely positive for any of these agents. In tests for intrapulmonary carcinogenicity from inhaled agents, therefore, the hamster has not been shown to have any uniquely useful role.

The importance of this review is demonstrated by the number of agents for which the only evidence for intrapulmonary cancer hazard comes from positive results from the rat. Tables 2 to 5 list 18 particles, mixtures, or gases with positive or limited results in rats for which there are no data or are negative data from other animals and no reported evidence of lung carcinogenicity in humans. These 18 agents include some for which there are no data useful for judging human lung carcinogenicity (e.g., aramid fibers), and at least one (coal dust) for which a convincingly large negative data base exists. The apparent propensity of the rat lung for tumorigenesis when exposed chronically to high concentrations of solid particles seems to justify the concern that, especially under exposure conditions more severe than expected for humans, results from rats may produce falsely positive indications of lung cancer hazard.

**Differences between Rats and Other Species in Lung Responses to Particles**

Additional insight into the potential usefulness of the rat as an inhalation carcinogenesis model can be gained by comparing the histological responses of the lungs of rats and other species to inhaled particles. An understanding of the comparative pattern of particle accumulation in the lung and the acute and chronic cellular responses and their genetic bases would be helpful in selecting the most appropriate bioassay models. Ideally, the responses of the rat lung would be compared in detail to those of humans exposed heavily to the same particles, but the ability to do this is presently limited. This section presents information that suggests indirectly that the rat may differ from humans in fundamental ways in the effects of particles in the lung.

**Retention of Deposited Particles.** Two recent reviews suggest that differences in the pattern of intrapulmonary particle retention may contribute to the known or suspected differences between the tumorigenicity of particles in lungs of rats and those of mice (4) and humans (97), respectively. The comparison to potential human retention patterns was limited to qualitative observations in nonhuman primates. Mauderly (4) recently reviewed information indicating that although diesel soot particles accumulated in lungs of both rats and mice in similar quantity in relation to lung size during chronic exposure, the pattern of accumulation differed. Soot was retained primarily in intra-alveolar macrophages in both species. Soot-filled macrophages tended to accumulate in focal areas near terminal bronchiolar–alveolar duct junctions in rats, but were somewhat more uniformly distributed throughout the lungs of mice. The foci of soot accumulation in rats were also the principal locations of inflammatory, epithelial proliferative, and fibrotic responses, which were much more pronounced in rats than in mice. It was hypothesized that the greater focal aggregation of soot-laden macrophages in rats contributed to their greater tissue responses. Similar differences between rats and mice have been observed for other particles (98).

Snipes (97) reviewed information suggesting that during chronic inhalation exposure, particles are retained to a greater degree in interstitial locations in lungs of nonhuman primates and dogs than in lungs of rats. Because there have been no lifetime inhalation exposures of dogs or nonhuman primates, this observation could not be linked directly to carcinogenesis. However, it was hypothesized that the interspecies difference in particle location might contribute to corresponding differences in tissue response.

More recently, Nikula et al. (99) performed quantitative analyses of the
histological location of particles in the lungs of rats and cynomolgus monkeys exposed in a 2-year study to either diesel soot or coal dust at 2 mg/m³ respirable dust. The low exposure concentration did not cause increased incidences of lung tumors in rats, and the exposure was too short to test for carcinogenicity in the monkeys; however, the study provided the most thorough comparison to date of the particle retention patterns in rats and non-human primates. The exposure material did not influence the retention patterns of either species despite the different compositions and particle sizes of the two materials. In rats, over 70% of the particles were found in intra-alveolar macrophages, while less than 30% were found in the interstitium and pulmonary pleura. In contrast, more than 50% of the particles were found in the interstitium and pulmonary pleura in monkeys. These quantitative results supported the observations of Snipes (97), which suggest that the same difference would likely be observed for other types of particles and other species (e.g., human dog) with more pronounced interstitial and pleural structures than rats.

Epithelial Hyperplasia. The intrapulmonary tumors induced in rats by heavy, chronic exposure to particles are thought to be of epithelial origin, and the most likely progenitor cells are the type II alveolar cells or the terminal bronchiole Clara cells (4,5,15). Although bronchogenic carcinomas are a common form of lung cancer in humans, adenocarcinomas in more distal locations are also observed (100). The finding that rat lung tumors often appear as a continuum of epithelial changes beginning with hyperplasia (5,100) suggests the importance of comparing proliferative responses of particle-exposed rats to those of other species.

The striking difference between the lung carcinogenicity of diesel soot in rats and mice (70) is paralleled not only by differences in particle retention as described above, but also by differences in epithelial hyperplasia in terminal bronchioles and alveoli. Mauderly et al. (101) exposed F344 rats and CD-1 mice 7 hr/day, 5 days/week to exhaust at a soot concentration of 7.1 mg/m³. After 18 months of exposure, terminal bronchiolar and alveolar epithelial cell replication was measured by labeling with tritiated thymidine (101). The labeling rate in terminal bronchioles in areas of soot retention was increased over 5-fold in rats but only 20% in mice (Figure 1). The labeling index of alveolar type II cells was increased over 8-fold in rats but only doubled in mice. Similar differences between rats and mice in epithelial hyperplasia have been observed for other particles, although there are few other quantitative data (98).

Nikula et al. (99) observed a striking difference in epithelial hyperplasia between rats and monkeys exposed to diesel soot or coal dust. As in other studies of diesel-exposed rats, they found marked hyperplasia of type II cells in alveoli containing particle-filled macrophages. There was no noticeable difference in response to the two types of particles. In contrast, they found very little hyperplasia in alveoli of monkeys exposed to either material. The most severe hyperplasia in alveoli containing particle-filled macrophages in monkeys consisted of only a few more type II cells than normal. This finding suggests that there is strikingly less epithelial response to inhaled particles in nonhuman primates than in rats, and perhaps even less than in mice. As we believe that epithelial hyperplasia is related to formation of epithelial tumors, it is reasonable to speculate that many dust exposures causing marked hyperplasia and late-occurring lung tumors in rats might not cause significant increases in intrapulmonary epithelial tumors in nonhuman primates if the latter were exposed for lifetime.

Another suggestion that the alveolar epithelium of rats may respond differently to chronic particle exposure than the epithelium of humans arises from the common development in rats of a keratinizing proliferative lesion seldom, if ever, found in other species. As mentioned in the introduction and reviewed previously (4,100), rats often develop a lesion called "squamous cyst" (5), "benign keratinizing cystic squamous cell tumor" (6), or "proliferative keratin cyst" (7) as a late-occurring response to extremely heavy particle exposure. This lesion is of interpretive importance because its inclusion as a benign tumor can result in a statistically significant response in some studies in which its exclusion might prevent the tumor response from reaching significance. Regardless of the terminology applied, this lesion is also important for its indication that the alveolar epithelium of the rat may be genetically predisposed toward proliferative and metaplastic responses uncharacteristic of other species. Despite equally heavy chronic particle exposures in other rodents, there has been only one report of a lesion in other rodents (a diesel soot-exposed mouse) that may resemble the lesion characteristic of rats (102). More importantly, there appears to be no corresponding lesion in dust-exposed humans (100). In aggregate, the above information suggests that under extreme exposure conditions, the responses of the rat alveolar epithelium to inhaled particles may not closely model the responses of human alveolar epithelium.

**Summary and Conclusions**

The relevance of particle-induced rat lung tumors to the assessment of human lung
cancer hazard and risk remains uncertain. Evidence suggests that the lung tumor responses of rats to heavy, chronic particle exposures may provide inaccurately high estimates of carcinogenic hazard, and may even provide false positives with respect to human lung cancer risk. This evidence includes knowledge that a) results from rats often cannot be extrapolated to estimate accurately the lung tumor risk in other rodents; b) the epithelial hyperplastic responses of rats cannot be extrapolated to predict accurately the proliferative responses in other animals; c) the limited evidence for the carcinogenicity of inhaled coal dust in rats conflicts with human experience; d) the pattern of particle retention differs between rats and nonhuman primates; and e) the epithelial proliferative response of rats, including squamous cysts, does not appear to model closely human epithelial responses to particles.

On the other hand, there is evidence supporting continued use of rats in exploration of carcinogenic hazards of inhaled particles and other agents. First, with the possible exception of nickel sulfate and to the extent of the agents tested, particulate agents known to be human lung carcinogens when inhaled are also carcinogenic in the lungs of rats. Mice and Syrian golden hamsters, however, have given false negatives. Second, rats are clearly the most sensitive of the three rodent species to intrapulmonary carcinogenesis from inhaled particles. Use of rats, therefore, should mitigate the risk of failure to detect a carcinogenic hazard.

It is not clear whether the use of another species, such as the mouse, greatly improves our ability to use results from rats to identify human lung cancer hazards. While positive results in both rats and mice should provide a greater certainty that the agent presents a potential carcinogenic hazard to humans, we do not presently have the ability to interpret with confidence a positive finding in either species in the presence of negative results in the other. We are now faced with several agents that are positive in rats and not tested in mice, and it appears reasonable to speculate that many additional particles might be positive in rats exposed chronically to sufficient concentrations. Whereas some studies have been negative in rats exposed to particles by inhalation, it may be that higher concentrations of these materials would have produced positive results.

It appears that at present we should continue to use rats in assays of the inhalation carcinogenicity hazard of particles and mixtures containing particles. However, the uncertainties associated with extrapolating results from rats to humans suggest that it is seldom, if ever, appropriate to estimate unit human lung cancer risks from rat lung tumor data. Assays of gases and vapors should include both rats and mice. It is not clear that the Syrian hamster has any usefulness for intrapulmonary carcinogenesis inhalation bioassays. We may someday be able to understand and predict similarities and differences in responses among species, including humans, on the basis of cellular or gene function, and studies of interspecies differences at the cellular level should be encouraged. At present, however, this remains a distant hope.

Although it appears wise at present to continue using rats in inhalation bioassays of particles, the upper limits of exposure should be selected carefully to mitigate the chance of false positives in rats due to excessively high concentrations of particles. For example, it may be appropriate to avoid exposures that result in particle accumulations in lungs of rats greater on a size-specific basis than the maximum accumulations estimated for humans under the most extreme expected conditions. Unfortunately, we have limited knowledge on which to base the maximum exposure concentration. Several attempts have been made to define strategies for setting the upper bound for exposure concentrations to particles, usually by defining effects that signal some form of maximum tolerated dose (103–106). Overall, it seems warranted to interpret with great caution the significance of rat lung tumorigenesis that results from particle exposures that exceed some low multiple of tissue-level dosing expected in humans, and multiple-dose studies should include at least one level sufficiently low to simulate an expected human exposure at the tissue level.

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