Comparative Carcinogenic Effects of Nickel Subsulfide, Nickel Oxide, or Nickel Sulfate Hexahydrate Chronic Exposures in the Lung


ABSTRACT

The relative toxicity and carcinogenicity of nickel sulfate hexahydrate (NiSO4·6H2O), nickel subsulfide (Ni5S2), and nickel oxide (NiO) were studied in F344/N rats and B6C3F1 mice after inhalation exposure for 6 h/day, 5 days/week, for 2 years. Nickel subsulfide (0.15 and 1 mg/m3) and nickel oxide (1.25 and 2.5 mg/m3) caused an exposure-related increased incidence of alveolar/bronchiolar neoplasms and adrenal medulla neoplasms in male and female rats. Nickel oxide caused an equivocal exposure-related increased incidence in alveolar/bronchiolar neoplasms in female mice. No exposure-related neoplastic responses occurred in rats or mice exposed to nickel sulfate or in mice exposed to nickel subsulfide. These findings are consistent with results from other studies, which show that nickel subsulfide and nickel oxide reach the nucleus in greater amounts than the water-soluble nickel compounds such as nickel sulfate. It has been proposed that the more water-insoluble particles are phagocytized, whereas the vacuoles containing nickel migrate to the nuclear membrane, where they release nickel ions that effect DNA damage. The findings from these experimental studies show that chronic exposure to nickel can cause lung neoplasms in rats, and that this response is related to exposure to specific types of nickel compounds.

INTRODUCTION

In 1932, the British Chief Inspector for Factories and Workshops reported an increase in respiratory tract cancer in workers in the nickel refinery in Wales (1). Further evidence that some hazard in the nickel refinery caused these cancers was published some 25 years later, and excess risks for respiratory cancer have been reported in other nickel industries in Canada, Norway, and Russia (2, 3). Nickel is primarily imported into the United States, where it is used in various industrial processes including fabrication of metal products, metal plating, and chemical and electric industries (4).

Cohorts of nickel-exposed workers continue to be studied to determine the parts and exposures of the refining processes that produce an increased risk for cancer. However, it has not been possible to characterize specific risks from nickel exposures because exposures may be multiple, including exposures to multiple nickel compounds, to other chemicals in the workplace, or to cigarette smoke or alcohol. Many of the studies that have found an association between nickel exposures and lung and/or nasal cancer have focused on “high-risk” cohorts. However, cancer was not found in all groups of exposed nickel workers (5, 6). Excess mortality from nonmalignant respiratory effects or other disease have not been seen in epidemiological studies.

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1. This research was conducted under Intergency Agreement Y01-ES-30108 between the National Institutes of Environmental Health Sciences and the United States Department of Energy. The in-life phase of the study was conducted at the Inhalation Toxicology Research Institute which is operated for the United States Department of Energy under contract DE-AC04-76EV00103. The facilities used for this research were fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

2. To whom requests for reprints should be addressed, at National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

3. The abbreviations used are: σg, approximate geometric SD; A/B, alveolar/bronchiolar; i.t., intratracheal.

that have shown an association between nickel exposure and cancer (5, 6).

We have previously reported the results of inhalation toxicity studies to nickel compounds commonly found in the workplace, including nickel subsulfide, nickel oxide, or nickel sulfate. The nickel oxide used in these studies was “high-temperature” nickel oxide, a type of nickel that may be formed during high-temperature operations such as in the stainless steel industry. In the F344 rat and B6C3F1 mouse, the major toxicity occurs in the lung after exposures to these nickel compounds. Nickel sulfate caused lung toxicity at lower exposure concentrations than did nickel subsulfide or nickel oxide (7). Comparisons of the carcinogenic effects between nickel compounds and differences in responses between rats and mice are described in this paper, and information is provided for comparing results in experimental models with those in humans.

MATERIALS AND METHODS

Chemicals. Nickel subsulfide (α-Ni5S2; MW, 240.2; CAS No. 12035-72-2) and nickel oxide (NiO; green oxide, calcined at 1350°C; MW, 74.7; CAS No. 1313-99-1) were supplied by the International Nickel Co., Ltd. (Toronto, Canada). Nickel sulfate hexahydrate (NiSO4·6H2O; referred to as nickel sulfate; MW, 262.9; CAS No. 10101-97-0) was obtained from Aldrich Chemical Co. (Milwaukee, WI). Elemental analysis conducted on these compounds by the Midwest Research Institute indicated overall purities of 97–99% (8–10). The range of mass median aerodynamic diameters and σg obtained throughout the study of Ni5S2, NiO, and NiSO4·6H2O were 2.0–2.2 μm (σg 2.0), 2.2–2.5 μm (σg 1.8), and 2.2–2.5 μm (σg 2.2), respectively.

Aerosol Characteristics. The exposure systems and methods for aerosol generation and characterization have been described previously (8–10). The animals were exposed in Hazleton 1000 (mice) and Hazleton 2000 (rats) whole-body chambers (Lab Products, Inc., Maywood, NJ) for 6 h/day, 5 days/week, for 102 weeks. Ni3S2 and NiO aerosols were generated using 2' and 4' fluid bed generators, respectively. Nickel sulfate aerosols were generated by nebulization of nickel sulfate solutions. Aerosol concentration was determined by taking three 2-h filter samples throughout the exposure day. Real-time determination of aerosol concentration was made using real-time aerosol monitor—model S units. Aerosol size was determined using cascade impactors.

Experimental Design. Core groups of 50 male and 50 female F344 rats (Taconic Farms, Germantown, NY) and 50 male and 50 female B6C3F1 mice (Simonsen Laboratories, Gilroy, CA) were exposed to nickel sulfate hexahydrate, nickel subsulfide, or nickel oxide for 6 h/day, five days/week, for 2 years (Table 1).

The high exposure concentrations for nickel oxide and nickel sulfate were selected based on the minimal to mild inflammatory lung lesions observed in the 13-week toxicity studies (7). In the nickel subsulfide study, the high exposure concentration (1 mg/m3) corresponded to that used in a previous nickel subsulfide study (11). The 0.15 mg/m3 concentration was selected based on the severity of inflammatory lung lesions in the 13-week studies, which corresponded to that observed in the high exposure level selected for the 2-year nickel oxide and nickel sulfate hexahydrate studies.

Additional animals were added for lung burden determinations at 7 or 15 months. Atomic absorption spectroscopy was used for determining nickel burdens in the lung according to methods described previously (12).

Food (NIH-07 Certified Diet; Ziegler Brothers, Inc., Gardiners, PA) was provided during nonexposure periods. Water was provided ad libitum. A 12-h
day/night cycle was maintained. Body weight and clinical signs were recorded every 4 weeks.

Pathology. Complete necropsies were done on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues and lesions were preserved in 10% neutral-buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination.

Statistical Evaluation. The majority of neoplasms were considered to be incidental to the cause of death or not rapidly lethal and were evaluated by logistic regression analysis (13, 14). Tests of significance included pairwise comparisons of each exposed group with controls and a test for overall exposure-related trends. Organ and body weight data were analyzed using parametric multiple comparison procedures (15, 16), and lung burden data were analyzed using nonparametric multiple comparison methods (17, 18). The reported values were considered significant at the \( P < 0.05 \) level.

RESULTS

Survival and Body and Lung Weights

Survival of rats and mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide were in general similar to those of controls. Final mean body weights in both rats and mice were similar or 5–10% lower than controls (Tables 2 and 3). Lung weights in exposed animals were greater than controls, and this was considered to be related to inflammatory lung reactions that occurred in response to these nickel exposures. The lung weights in the nickel oxide- and nickel subsulfide-exposed rats relative to controls were increased more than in mice and correlated with a more severe inflammatory and toxic response in the lung of rats at the exposure concentrations used in these 2-year studies.

The increase in lung weights of animals in the nickel subsulfide and nickel oxide studies was greater than in the nickel sulfate studies and correlated with a more severe inflammatory response after exposures to nickel subsulfide and nickel oxide. Nickel sulfate was more acutely toxic than nickel subsulfide or nickel oxide, causing death of animals at exposure concentrations of 2 mg/m³ in rats and 7 mg/m³ in mice as has been reported previously in subchronic studies (7).

At 15-months, the lung weight in the high-exposure nickel sulfate mice was 30–37% more than control lung weight, and in the rats, 33–41% more than controls; the high-exposure lung weight in the nickel subsulfide mice was 78–92% more than controls, and in rats, 300% more; in the nickel oxide studies the high-exposure lung weight in mice was 36–65% more than controls, and in rats, 86–94% more.

Noncarcinogenic Effects

A spectrum of exposure-related nonneoplastic respiratory tract lesions seen after exposure to each of the nickels included focal alveolar/bronchiolar hyperplasia, inflammation, and/or fibrosis of the lung and lymphoid hyperplasia of the lung-associated lymph nodes. Atrophy of the olfactory epithelium was also seen after exposure to nickel sulfate hexahydrate. Pigment (thought to represent nickel deposition) was also observed in the lung of animals exposed to nickel oxide. Qualitatively, the inflammatory responses of interstitial fibrosis and intraalveolar macrophage accumulation in the lung were similar in the three nickel compounds studied. However, at the exposure concentrations used, these toxic lesions were considered to be more severe after exposure to nickel oxide and nickel subsulfide. Mice were more resistant to development of focal hyperplastic and fibrotic lung lesions than were rats.

Carcinogenic Effects

Nickel Oxide Studies. There was an increase in the incidence of A/B adenomas/carcinomas combined (A/B neoplasms) in male and female rats exposed to nickel oxide at concentrations of 1.2 and 2.5 mg/m³ (Table 4). A slight increase in A/B adenomas occurred in female mice exposed to 2.5 mg/m³. An increase in A/B adenomas/carcinomas combined occurred in female mice exposed to 1.2 mg/m³ (Table 5).

The carcinogenic response in the lung of male and female rats exposed to nickel oxide was related to exposure because (a) the incidence of A/B neoplasms was increased in both mid- and high-
exposure groups relative to concurrent and historical control rates, and 
(b) the effects were observed in both male and female rats. A marginal 
increase in A/B neoplasms was seen at the low and mid exposure 
levels in female mice.

**Nickel Subsulfide Studies.** There was an increase in the incidence 
of A/B adenomas, A/B carcinomas, and A/B adenoma/carcinomas 
combined in male rats exposed to 1 mg/m³. The incidences of A/B 
adenomas/carcinomas combined in male rats exposed to 0.15 mg/m³ 
levels in female mice.

The carcinogenic response in the lung of male and female rats 
exposed to nickel subsulfide was clear evidence for a carcinogenic 
effect because neoplastic lung lesions were observed at both exposure 
levels, the effect was observed in males and females, and the incidence 
for these neoplasms was increased relative to concurrent and 
historical control rates.

**Nickel Sulfate Studies.** There were no increases in lung neoplasms 
in rats or mice exposed to nickel sulfate (Tables 4 and 5). The A/B 
neoplasms that were observed in the exposed groups were similar in 
incidence and morphology to those observed in controls.

**Description of Lung Neoplasms**

The A/B neoplasms in mice and in some rats in the nickel subsulfide 
and nickel oxide studies had morphology consistent with spontaneously occurring lung neoplasms in rodents. Typically, most A/B 
carcinomas had cuboidal or low columnar epithelium in mixtures of tubular, papillary, and alveolar growth patterns. Neoplastic cells in 
carcinomas were pleomorphic and often stained deeply basophilic. 
Focal alveolar epithelial hyperplasia was part of the morphological continuum toward neoplasia and consisted of discrete areas where 
alveoli were lined by cuboidal cells that occasionally formed small projections within alveolar lumens.

Some of the A/B neoplasms in rats exposed to nickel subsulfide or 
nickel oxide had morphological features that differed from the typical papillary or solid neoplastic proliferations of A/B epithelium typically 
found in control rats. Different morphological features included a prominent fibrous tissue component (Fig. 1) and/or areas of differentiation to stratified squamous epithelium in A/B carcinomas (Fig. 2). 
In addition, inflammatory cells, cellular debris, and areas of squamous differentiation or a prominent dense fibrous tissue component occurred in some A/B adenomas.

**Other Carcinogenic Effects**

A carcinogenic response was also seen in the adrenal medulla of 
nickel subsulfide and nickel oxide rats (Table 6). There were no other sites for exposure-related increases in neoplasms in rats or in mice 
after exposure to nickel sulfate, nickel oxide, or nickel subsulfide.

**Lung Burden Data**

Analysis of the nickel lung burden data showed accumulation of 
nickel in the lungs of rats and mice after exposure to nickel oxide, 
whereas with nickel subsulfide and nickel sulfate, nickel was cleared from the lungs. The lung burden at 7 or 15 months in rats and mice 
was 1–2 μg Ni/g lung for nickel sulfate, 3–26 μg Ni/g lung for nickel 
subsulfide, and 175–2,258 μg Ni/g lung for nickel oxide (Table 7). 
The lungs were enlarged particularly in the exposed groups of rats in

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**Table 3. Survival, body weight, and lung weight in mice.**

<table>
<thead>
<tr>
<th>Exposure (mg/m³)</th>
<th>Nickel sulfate hexahydrate (22.3% nickel)</th>
<th>Nickel subsulfide (73.3% nickel)</th>
<th>Nickel oxide (78.6% nickel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male mice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>26/61</td>
<td>25/59</td>
<td>26/58</td>
</tr>
<tr>
<td>Absolute lung weight</td>
<td>94</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>7-Month interim</td>
<td>0.21</td>
<td>0.22</td>
<td>0.34</td>
</tr>
<tr>
<td>15-Month interim</td>
<td>0.21</td>
<td>0.26</td>
<td>0.31</td>
</tr>
<tr>
<td>Female mice</td>
<td>34/61</td>
<td>34/59</td>
<td>38/58</td>
</tr>
<tr>
<td>Absolute lung weight</td>
<td>91</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

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**Table 4. Alveolar/bronchiolar neoplasms in rats.**

<table>
<thead>
<tr>
<th>Exposure (mg/m³)</th>
<th>Nickel sulfate hexahydrate (22.3% nickel)</th>
<th>Nickel subsulfide (73.5% nickel)</th>
<th>Nickel oxide (78.6% nickel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>54</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Adenoma/carcinoma</td>
<td>2</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Female rats</td>
<td>52</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Adenoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Adenoma/carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a* Percent relative to controls. 
*b* Organ weight in grams. 
*c* dp < 0.05. 
*d* dp = 0.01. 
*e* dp = 0.05.
the nickel oxide and nickel subsulfide studies. Therefore, when the rat lung burden data at 7 or 15 months are expressed as amount of nickel per total lung, the nickel accumulation after nickel oxide exposures is emphasized: 1–2 μg Ni/lung for nickel sulfate; 9–29 μg Ni/lung for nickel subsulfide; and 226–4573 μg Ni/lung for nickel oxide.

DISCUSSION

The most significant findings from these studies were that nickel subsulfide and nickel oxide caused lung neoplasms in rats, and nickel oxide caused a marginal increase in lung neoplasms in mice (Table 8). There was also inflammation, hyperplasia, and fibrosis in the lungs of rats, and to a lesser extent in mice, exposed to all three nickel compounds. No exposure-related lung neoplasms occurred in rats or mice in the nickel sulfate studies.

In the nickel subsulfide rats, there were increases in lung neoplasms at 0.15 and 1.0 mg/m³ (0.11 and 0.73 mg Ni/m³) and in the nickel oxide rats at 1.25 and 2.5 mg/m³ (1.0 and 2.0 mg Ni/m³) after nickel exposures of more than 1 year. As a point of reference, the threshold limit value for insoluble nickel compounds is 1 mg Ni/m³, although most work situations would involve lower nickel exposures (19).

The type of nickel compound is important in the eventual carcinogenic response. Under the conditions of these studies, the nickel compound that was more rapidly cleared from the lungs (nickel subsulfide) gave a stronger carcinogenic response than the nickel compound retained in the lungs (nickel oxide). Thus, the amount of nickel in the lung (which represents the difference between the amount of nickel deposited in the lung and the amount removed by the clearance mechanisms) does not predict the severity of the lung tumor response. In these studies, nickel sulfate and nickel subsulfide were cleared from the lung, whereas nickel oxide accumulated. This agrees with previous studies, which showed that the half-life of nickel sulfate in the rat lung is 1–3 days (20), that of nickel subsulfide, 5 days, and that of nickel oxide, approximately 120 days (21).

In humans, it has also been shown that the amount of nickel retained in the lung may not predict the carcinogenic response after nickel exposure. In lung tissue specimens from 39 workers in the nickel industry (22), the average nickel concentration for workers in roasting and smelting operations was 330 ± 380 μg nickel/g dry lung weight; for workers in electrolysis departments, 34 ± 48 μg/g; and for unexposed people, 0.76 ± 0.39 μg/g (dry lung represents approximately 20% “wet” lung weight, the lung weight used in our studies in rodents). Workers who were diagnosed with lung cancer (14 cases) had the same lung nickel burdens at autopsy as did nickel workers (25 cases) who died of other causes. This study also found that lung cancer occurred in workers from the electrolysis department (8 of 24), as well as those from the roasting and smelting operations (6 of 15), although those from the electrolysis department had lower lung nickel burdens. Thus, both our studies and the studies in humans show that a measurement of retained nickel does not necessarily predict the extent of lung cancer after nickel exposures.

The formation of lung neoplasms in rodents after exposures to nickel subsulfide and nickel oxide were considered to be specifically related to the nickel exposures. Nickel subsulfide lung burdens at 15 months remained below 30 μg Ni/g lung, but nickel lung burdens increased in the nickel oxide studies to approximately 1000 μg Ni/g lung (>4000 μg Ni/lung). The possible relationship between nickel accumulation in the lung in the nickel oxide studies and the toxicological effects remains unclear at this time. Recent studies have shown that repeated exposure to 0.62 and 2.5 mg NiO/m³ results in impaired clearance of subsequent inhaled nickel oxide (23).

Rat carcinogenicity studies with other relatively nontoxic particles, such as titanium dioxide [250 mg/m³ (24)], talc [18 mg/m³ (25)], and antimony trioxide [45 mg/m³ (26)], required higher aerosol concentrations to produce a carcinogenic response than did the nickel compounds. For example, the carcinogenic response in the rat lung in talc studies was seen at 18 mg/m³, and at this exposure, lung burden was approximately 25 mg talc/g lung at 18 and 24 months. The lung tumor response with these other substances may be due in part to accumulation of nontoxic particles.

Other studies have shown that nickel subsulfide is carcinogenic in the rat after local injection (5), inhalation exposure (1 mg/m³) (11), and i.t. administration (27, 28), but not after i.t. administration in hamsters (29). Nickel oxide has been shown to be carcinogenic after local injection in rodents, but there have been no previous chronic inhalation studies with this compound in rats. One long-term nickel oxide inhalation study performed in hamsters (50 mg/m³) was negative for carcinogenic activity (30). In contrast, nickel sulfate does not produce tumors after local injection (5). Therefore, it appears that for the nickel compounds used in these studies, the carcinogenic response after local injection predicts the carcinogenic response after inhalation exposure in the rat.

Selection of the model system is important in assessing and predicting the potential extent of environment disease. More chemical-related lung neoplasms were observed in nickel subsulfide- and nickel oxide-exposed rats than in mice. In studies of other metals (e.g.,

Fig. 1. Alveolar/bronchiolar carcinoma from a male rat exposed to 0.15 mg/m³ nickel subsulfide for 2 years. Note the extensive connective tissue between the neoplastic epithelial cells. ×240.

Fig. 2. Alveolar/bronchiolar carcinoma with areas of squamous differentiation from a male rat exposed to 1.0 mg/m³ nickel subsulfide. ×150.
Table 5 Alveolar/bronchiolar neoplasms in mice

<table>
<thead>
<tr>
<th>Exposure (mg/m³)</th>
<th>Nickel sulfate hexahydrate (22.3% nickel)</th>
<th>Nickel subsulfide (73.3% nickel)</th>
<th>Nickel oxide (78.6% nickel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male mice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>61a</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Adenoma/carcinoma</td>
<td>9</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Female rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>61a</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Adenoma/carcinoma</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Number of animals examined.

Table 6 Adrenal medulla proliferative lesions in rats

<table>
<thead>
<tr>
<th>Exposure (mg/m³)</th>
<th>Nickel sulfate hexahydrate (22.3% nickel)</th>
<th>Nickel subsulfide (73.3% nickel)</th>
<th>Nickel oxide (78.6% nickel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>54a</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Benign pheochromocytoma</td>
<td>28</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Malignant pheochromocytoma</td>
<td>0</td>
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<tr>
<td>Female rats</td>
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<td></td>
<td></td>
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<tr>
<td>Hyperplasia</td>
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<td>53</td>
<td>54</td>
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<td>Benign pheochromocytoma</td>
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<td>8</td>
</tr>
<tr>
<td>Malignant pheochromocytoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of animals examined.

Nasopharyngeal carcinoma in humans has been attributed to nickel exposure (6). In our studies, there was no evidence of carcinogenesis in the nasal cavity in either rats or mice. The preponderance of these sinonasal neoplasms in humans have been classified as anaplastic, undifferentiated, or squamous cell carcinoma (33). In nickel sulfate (prechronic and chronic) and nickel subsulfide (prechronic) inhalation rodent studies (7), the olfactory epithelium, rather than the respiratory or squamous mucosa, was the target site for chemical-related toxicity.

Table 7 Lung burden analyses in the studies of nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide

<table>
<thead>
<tr>
<th>Exposure (mg/m³)</th>
<th>Nickel sulfate hexahydrate (22.3% nickel)</th>
<th>Nickel subsulfide (73.3% nickel)</th>
<th>Nickel oxide (78.6% nickel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male mice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female mice</td>
<td></td>
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</tbody>
</table>

Results were below the limit of detection.

Values represent mean amount of nickel (μg nickel/g lung). Lung burden groups included 5–7 animals.
solvable nickel salts have a synergistic role in enhancing carcinogenesis after exposure to other nickel compounds.

The mechanisms for how nickel compounds cause carcinogenic effects is an area of continuing investigation. In vitro studies have shown that water-insoluble nickel compounds are more readily phagocytized than the water-soluble nickel compounds and, therefore, will reach the nucleus of the cell in greater amounts than will the water-soluble nickel compounds (35-40). Nickel subsulfide produces a high level of oxidants in the nuclei of cells, which could directly damage protein and DNA (41, 42). Other in vitro studies suggest that nickel may cause gene alterations by enhanced DNA methylation and heterochromatin condensation, causing inactivation of critical tumor suppressor or senescence genes (43, 44).

Our findings of the carcinogenic response in the rat lung after exposure to nickel subsulfide or nickel oxide agree with epidemiology findings, which show that exposure of workers particularly to the oxidic and sulfidic nickel compounds may lead to an increased risk of lung cancer (6). The epidemiology studies also suggest that exposure to soluble nickel salts enhances the risk associated with exposure to less soluble forms of nickel.

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