3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

In a study undertaken by the National Toxicology Program (2000), groups of 50 male and 50 female B6C3F$_1$ mice, 6 weeks of age, were exposed by inhalation to gallium arsenide particulate (purity, > 98%; MMAD, 0.9–1.0 μm; GSD, 1.8–1.9 μm) at concentrations of 0, 0.1, 0.5 or 1 mg/m^3 for 6 h per day, 5 days per week, for 105 weeks (males) or 106 weeks (females). No adverse effects on survival were observed in exposed males or females compared with chamber controls (survival rates: 35/50 (control), 38/50 (low dose), 34/50 (mid dose) and 34/50 (high dose) in males and 36/50, 34/50, 31/50 or 29/50 in females, respectively; mean survival times: 687, 707, 684 or 701 days in males and 699, 699, 665 or 682 days in females, respectively). There was no evidence of carcinogenic activity in male or female mice exposed to gallium arsenide; however, exposure did result in the development of a spectrum of inflammatory and proliferative lesions of the respiratory tract of mice (National Toxicology Program, 2000) (see Section 4.3).

3.1.2 *Rat*

In a study undertaken by the National Toxicology Program (2000), groups of 50 male and 50 female Fischer 344/N rats, 6 weeks of age, were exposed by inhalation to gallium arsenide particulate (purity, > 98%; MMAD, 0.9–1.0 μm; GSD, 1.8–1.9 μm) at concentrations of 0, 0.01, 0.1 or 1 mg/m^3 for 6 h per day, 5 days per week, for 105 weeks. No adverse effects on survival were observed in treated males or females compared with chamber controls (survival rates: 13/50 (control), 13/50 (low dose), 15/50 (mid dose) and 13/50 (high dose) in males and 19/50, 17/50, 21/50 or 11/50 in females, respectively; mean survival times: 651, 627, 656 or 636 days in males and 666, 659, 644 or 626 days in females, respectively). Mean body weights were generally decreased in males exposed to the high dose throughout the study and slightly decreased in females exposed to the same dose during the second year compared with chamber controls. Although there was no evidence of carcinogenic activity in male rats exposed to gallium arsenide, exposure did result in the development of a spectrum of inflammatory and proliferative lesions of the respiratory tract (see Section 4.3). A clear neoplastic response was observed in the lung and the adrenal medulla of female rats. Increased incidence of mononuclear cell leukaemia was also observed. However, exposure to gallium arsenide did not cause an increased incidence of neoplasms in other tissues. The incidence of neoplasms and non-neoplastic lesions in female rats is reported in Table 2.

Table 2. Incidence of neoplasms and non-neoplastic lesions in female rats in a 2-year inhalation study of gallium arsenide

	No. of rats exposed to gallium arsenide at concentrations (mg/m^3) of			
	0 (chamber control)	0.01	0.1	1.0
Lung				
Total no. examined	50	50	50	50
No. with:				
Cyst, squamous	0	0	1 (4.0)	0
Hyperplasia, atypical	0	0	9[b] (2.2)	16[b] (2.2)
Inflammation, chronic active	11 (1.1)[a]	46[b] (1.5)	49[b] (2.8)	50[b] (3.7)
Metaplasia, squamous	0	0	2 (2.5)	1 (2.0)
Proteinosis	1 (1.0)	24[b] (1.0)	47[b] (2.2)	49[b] (3.8)
Alveolar epithelium, hyperplasia	14 (1.5)	9 (1.6)	17 (2.1)	14 (2.3)
Alveolar epithelium, metaplasia	0	1 (1.0)	36[b] (2.4)	41[b] (2.6)
Alveolar/bronchiolar adenoma				
Overall rate	0	0	2	7[b]
Alveolar/bronchiolar carcinoma				
Overall rate	0	0	2	3
Alveolar/bronchiolar adenoma or carcinoma				
Overall rate	0	0	4	9[b]
Squamous-cell carcinoma	0	0	0	1
Adrenal medulla				
Total no. examined	50	49	50	49
No. with:				
Hyperplasia	16 (2.0)	11 (1.8)	16 (1.8)	12 (2.5)
Benign pheochromocytoma	4	5	6	13[b]
Malignant pheochromocytoma	0	1	0	0
Mononuclear cell leukaemia				
Overall rate	22	21	18	33[c]

From National Toxicology Program (2000)

[a] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked

[b] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test

[c] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test

In female rats, exposure to gallium arsenide caused a broad spectrum of proliferative, non-proliferative, and inflammatory lesions in the lungs, including a concentration-related increase in the incidence of alveolar/bronchiolar adenoma, and alveolar/bronchiolar adenoma and carcinoma (combined). Benign and malignant neoplasms of the lung

occurred in an exposure concentration-related manner in female rats. An increased incidence of atypical hyperplasia of the alveolar epithelium was observed in both male and female rats. Most lesions identified as atypical epithelial hyperplasia were irregular, often multiple, lesions that occurred at the edges of foci of chronic active inflammation. The incidence of alveolar epithelial metaplasia was significantly increased in females exposed to 0.1 or 1.0 mg/m^3 gallium arsenide. Alveolar epithelial metaplasia generally occurred within or adjacent to foci of chronic active inflammation and was characterized by replacement of normal alveolar epithelial cells (type I cells) with ciliated cuboidal to columnar epithelial cells. The incidences of chronic active inflammation and alveolar proteinosis were significantly increased in all exposed females, and severity of these lesions increased with increasing exposure concentration. Gallium arsenide particles were observed in the alveolar spaces and in macrophages, primarily in animals exposed to the higher concentrations.

Squamous metaplasia was present in a few gallium arsenide-exposed males and females and was usually associated with foci of chronic active inflammation. In one male in the high-dose group and one female in the mid-dose group, the squamous epithelium formed large cystic lesions diagnosed as squamous cysts. Although squamous epithelium is not a component of the normal lung, it often develops as a response to pulmonary injury associated with inhalation of irritants, especially particulates. One female in the high-dose group had an invasive squamous-cell carcinoma. The incidence of benign pheochromocytoma occurred in a dose-related manner in females and the incidence in females exposed to 1.0 mg/m^3 gallium arsenide was significantly increased compared to the chamber controls. Relative to chamber controls, the incidence of mononuclear cell leukaemia was significantly increased in females exposed to 1.0 mg/m^3. Mononuclear cell leukaemia is a common spontaneous neoplasm in Fischer 344/N rats and presents characteristically as a large granular lymphocytic leukaemia (National Toxicology Program, 2000).

3.2 Intratracheal instillation

Hamster

In a study by Ohyama and colleagues (1988), groups of 33 male 6-week old Syrian golden hamsters received weekly intratracheal instillations of 0 or 0.25 mg/animal gallium arsenide in 200 μL phosphate buffer [particle size and purity of vehicle not provided] for 15 weeks and were observed for 111–730 days. Gallium arsenide instillations significantly reduced survival (by 50%) at 1 year (mean survival time, 399 days versus 517 days in controls) and caused an increased incidence of alveolar cell hyperplasia (14/30) compared with controls (5/30). [The Working Group noted the low dose used, the short exposure duration, the small number of animals and the high mortality in the first year.] However, histopathological examination (larynx, trachea, lungs, liver, spleen, gastric tract, kidneys, bladder, and other tissues not further specified) of 30 hamsters that had died or been killed

gave no indication of an increased incidence of neoplasms (Ohyama *et al*., 1988). [The Working Group noted the inadequate reporting of the study and also judged the study design inadequate for carcinogenic effect determination.]