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Comparative Study of The Toxic Effects of Gallium Arsenide, Indium Arsenide and Arsenic Trioxide Following Intratracheal Instillations to The Lung of Syrian Golden Hamsters

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Abstract Toxic effects of gallium arsenide (GaAs), indium arsenide (InAs) and arsenic trioxide (As_2O_3) were studied in male Syrian golden hamsters. GaAs (7.7 mg/kg) and As_2O_3 (1.3 mg/kg) particles were instilled intratracheally twice a week a total of 16 times, while InAs (7.7 mg/kg) was instilled a total of 14 times. As a control, hamsters were treated with the vehicle, phosphate buffer solution. During the instillation period, the cumulative body weight gain of the InAs-, but not the GaAs- or As_2O_3-treated hamsters was suppressed significantly, when compared with the control group. Slight to severe inflammatory responses were observed in the lung for all treatment groups. The most severe inflammatory change, characterized by an accumulation of neutrophils and macrophages, exudation, thickness of the pleura and fibrotic proliferation was found in the InAs-treated hamsters. Extensive alveolar or bronchiolar cell hyperplasia with or without keratinizing squamous cell metaplasia was observed in almost all the InAs-treated hamsters. Furthermore, squamous cell metaplasia or squamous cell hyperplasia developed in some of the InAs-treated hamsters, but not in the GaAs- or As_2O_3-treated hamsters. Slight to mild lesions were found in the convoluted tubules of the kidney in both the GaAs and InAs groups.

From the present study, the toxic potency of these particles was provisionally estimated to be in the following order: InAs > GaAs > As_2O_3, at the dosage level used in this study. Furthermore, there was evidence that InAs particles could induce pulmonary, renal or systemic toxicity, and as such, InAs particles may produce pulmonary precancerous change when instilled intratracheally into hamsters.

Key words: semiconductor materials, gallium arsenide, indium arsenide, arsenic trioxide, lung toxicity, hamster, intratracheal instillations

Introduction

Gallium arsenide (GaAs) and indium arsenide (InAs) belong to the group of Ⅲ-Ⅴ compounds which make up these semiconductor materials[4)21)]. GaAs and InAs contain either the element arsenic, which is a highly toxic chemical suspected of being tumorigenic[10)12)], or gallium and indium which are toxic to the kidney, liver and lung[6)32)]. The increased use of these materials has gained attention due to potential occupational or environmental exposure.

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Although some studies concerning the environmental monitoring of hazardous materials have been conducted in semiconductor industries[5)23)], there is a shortage of available data regarding the health risks to employees in the semiconductor and its waste material disposal industries.

There have been some animal studies concerning the toxicity of semiconductor materials to the respiratory tracts. Goering et al.[8)] and Webb et al.[29)~31)] reported the acute pulmonary toxicity of GaAs particles when administered to the trachea of rats via a single instillation. Furthermore, Ohyama et al.[16)] revealed a significant reduction in the survival rate among hamsters treated with GaAs particles by intermittent intratracheal instillations during a 2-year observation period. On the other hand, Zheng et al.[36)] mentioned that indium was poorly absorbed from the digestive tract and that it was mostly excreted in the feces following multiple doses of oral administration or intratracheal instillation of indium phosphide (InP) in rats. Uemura et al.[27)] and Oda[15)] reported that a high or low dose of InP particles caused pulmonary inflammation in rats for 7 or 8 days following intratracheal instillation of InP particles. Our previous study[25)] reported that InAs and InP produced severe damage to the lungs of hamsters which received these particles through intermittent intratracheal exposure.

Although the prominent exposure route of most concern to humans is inhalation, extensive toxicological research using the intratracheal instillation method has been conducted to estimate the pulmonary toxicity of many hazardous particles or fibers since such studies are relatively inexpensive, uncomplicated, and enable the instillation of large amounts of these materials. In our previous studies[16)25)], we reported the chronic pulmonary toxicity of GaAs or InAs particulates with a relatively large diameter fraction when given via intermittent intratracheal instillations to hamsters.

In this study, we evaluated the comparative toxic effects of GaAs and InAs particles, which comprised fractions with a smaller particle diameter than those used in our previous study[25)], and arsenic trioxide (As_2O_3), comparing the toxicity of these insoluble inorganic arsenic compounds. In particular, we focused on the pulmonary toxicity of these particles, when instilled repeatedly to the trachea of hamsters.

Methods

Materials

GaAs and InAs, both of which had a purity of more 99.9999%, were obtained from Mitsuwa Chemicals (Osaka, Japan). As_2O_3 (special grade, >99.8%) and phosphate buffer solution (0.025M, pH 6.9) were purchased from Katayama Chemicals (Osaka, Japan). The samples of GaAs or InAs particles were prepared according to the method of Omura et al.[17)]. These particles were finely pulverized and were passed through a 400-mesh microsieve. The mean diameter of the GaAs particles was 1.32 μm, with a σg (geometric standard deviation) of 1.76, while that of the InAs particles was 1.58 μm, with a σg of 2.15. The GaAs sample contained 0.02% (wt%) of zirconium and a trace of yttrium, while the InAs sample contained 0.01% of zirconium and 0.01% of yttrium, which could have been due to adulteration from the planet ball mill used for pulverization.

Animals

All thirty male Syrian golden hamsters, from the colony of Japan SLC Inc., Hamamatsu, Japan, were purchased at 6 weeks of age. The hamsters were raised in the conventional conditioning room of the Laboratory of Animal

Experiments, Faculty of Medicine, Kyushu University, for six weeks until the beginning of the experiment. The light cycle was 12 hours: 12 hours (light/dark), the temperature was 23-25°C, and the air humidity was 50-60%. Four hamsters were housed in one stainless steel cage and fed a commercial diet (CE-2 pellets, Clea Japan Inc., Tokyo, Japan), with drinking tap water available *ad libitum*.

Treatment

The hamsters comprised four groups: the GaAs group, the InAs group, the As_2O_3 group and a control group. All groups comprised 8 hamsters except for the As_2O_3 group of 6 hamsters. The average body weight (mean±SE) at the beginning of the instillation was 124.9±10.36 g (range 104.2-148.5 g). The intratracheal instillations were carried out on 12-weeks-old hamsters which were given 0.1 ml/animal of atropine sulfate s. c. before being anesthetized with diethyl ether in a desiccator. Each test material was suspended in 1.0 ml/kg phosphate buffer solution and instilled into the trachea of the anesthetized hamsters twice a week, a total of 16 times except for the InAs group, by means of a 1-ml syringe with an oral administration probe suitable for mice. During the instillation period of the InAs-treated hamsters, three hamsters died, while the five surviving hamsters demonstrated a remarkable loss in body weight caused by the toxicity of the instilled material, and thus treatment was terminated after 14 instillations. Each instillation per animal comprised 7.7 mg/kg as GaAs or InAs particles, or 1.3 mg/kg as As_2O_3. The control hamsters received 1.0 ml/kg of phosphate buffer solution only. The total dose of GaAs particles (123.2 mg/kg, range 14.0-16.3 mg/animal) was almost the same as the single intratracheal instillation dose of Webb et al.[30] while that of As_2O_3 particles (20.8 mg/kg, range 2.7-3.1 mg/animal) was almost one half that given in the study of Yamamoto et al.[33].

Body weight was measured at the time of each instillation. All the surviving hamsters were euthaniazed by etherization on the day subsequent to their final instillation, and were then autopsied. Blood was collected from the posterior vena cava and serum was separated.

These experiments were conducted according to the Guidelines for Animal Experiments in Faculty of Medicine, Kyushu University and The Law (No. 105) and Notification (No. 6) of the Government of Japan.

Histopathological examination

The left lobe and right posterior lobe of the lung, half the spleen, part of the liver (except for the left lobe), and the right kidney were used for histopathological examination. These visceral organs were fixed in 10% neutral buffered formalin solution. The remaining organs and part of the serum were stored at −20°C, and were utilized as samples for metal analysis. Evaluation of the testicular toxicity of these tested materials and data regarding the metal concentration for each organ have already been reported by Omura et al.[18] and by Hirata et al.[9]. Fixed tissues were embedded in paraffin, cut into 6-μm sections, and stained with hematoxylin and eosin. Selected sections were stained with periodic acid Schiff (PAS), Elastica-van-Gieson and Masson's trichrome.

Statistical analysis

Fisher's least significant difference procedure was used in the cases of body weight gain and organ weight after a one-way analysis of variance. In all the statistical comparisons, a p value of less than 0.05 was used to indicate significant differences.

Results

Body weight change

Cumulative average body weight increase in each group following the initial instillation (0 g: body weight at first instillation) are shown in Fig. 1. After the eighth instillation, a remarkably suppressed body-weight gain was observed in the InAs group compared with the control group, which was statistically significant. Since the mean body weight gain of the InAs-treated hamsters showed a 5.43 g decrease (SE: 8.95) from that at the first instillation, while the surviving hamsters (n=5) showed a marked general weakening at the 14th instillation, subsequent treatment was discontinued at that time in the InAs group alone. Although there was some depressed mean body weight gain in the two other experimental groups during the instillation period (i. e. mean±SE at the 16th instillation; 32.36±3.97 g in the GaAs group, 35.05±4.12 g in the As_2O_3 group vs 38.44±5.24 g in the control group), there was no significant difference in the trend of body weight gain between the GaAs or As_2O_3 groups and the control group.

Organ weight

Fig. 2 shows the mean relative organ weights (g/100 g body weight) in each group compared with that in the control group. A significant increase in lung weight was observed in the 3 treatment groups compared with the control group. Although the lung relative weight in the As_2O_3-treated hamsters was almost 1.2 times greater than that in the controls, it was almost 2.1 or 4.3 greater than the controls in the GaAs- and InAs-treated hamsters. The relative weights of the spleen and kidney of the InAs-treated hamsters only were significantly increased compared with those of the control group. The weight of the liver in the GaAs, InAs and As_2O_3 groups was significantly lowered by 0.92, 0.8 or 0.89 times, compared with that in the control group.

Histopathology of the lung

The severity of inflammatory change of the

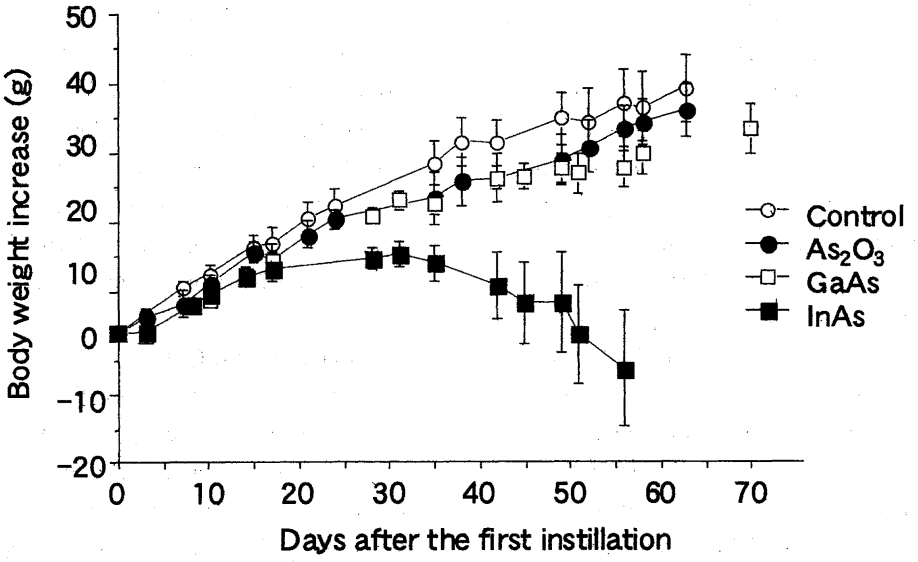

Fig. 1 Change in body weight gain from the time of the first instillation in each group

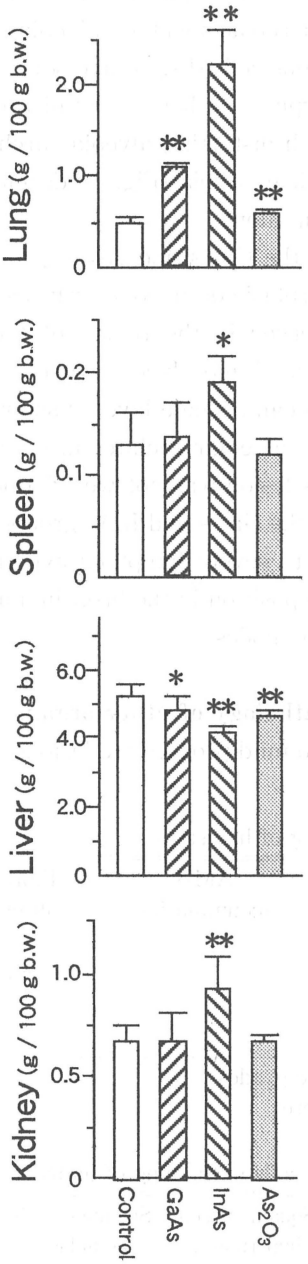

Fig. 2 Relative organ weight in each group. Significantly different from the control; *$p<0.05$, **$p<0.01$.

lung in each group is shown in Table 1. Foci of mild to severe inflammatory responses were present in the lungs in all groups. In these groups, inflammatory cells mostly consisted of neutrophils mixed with lesser numbers of alveolar mecrophages, plasma cells or lymphocytes, which were seen within the alveolar spaces, alveolar septa, bronchiolar lumens or peribronchiolar or perivascular tissues. Inflammation was increased in severity among the lnAs-treated hamsters. In the InAs group, extensive inflammatory foci were scattered throughout the lungs, and numerous neutrophils, necrotic cell debris, and alveolar macrophages either containing or not containing InAs particles were present within the alveolar septa, alveolar spaces or bronchiolar lumens. Exudations infiltrated the alveolar spaces including necrotic alveolar macrophages, partially showing PAS-positive. Furthermore, considerable alveolar macrophages remained adherent to the alveolar walls which became markedly thickened, revealing swelling with foamy cytoplasm. As for the alveolar macrophages which had infiltrated the alveolar spaces, although their number was relatively small when considering the degree of deposition of InAs particles, most of them showed swelling, degeneration or disintegration. In these regions of severe inflammation, there was severe interstitial fibrosis where Masson trichrome-stained sections revealed augmented collagen.

In the GaAs group, the inflammatory findings were similar to those observed in the InAs group, although the degree of response to the lung tissue was weaker compared that in the InAs group.

In the As_2O_3 group, inflammatory response was weaker than that in the GaAs group. As_2O_3 particles, exudation and alveolar macrophages were almost not present in the alveolar

walls, alveolar spaces or bronchiolar lumens.

Hyperplastic lesions of the alveolar or bronchiolar cells in the lung are described in Table 2. These lesions were classified into 4 types according to the International Classification of Rodent Tumours[11]. Lesions of mild to severe hyperplasia of alveolar or bronchiolar cells were observed in all groups, except for the control group.

In the InAs group, the most severe hyperplastic lesions with or without squamous cell hyperplasia were seen focally involving the alveoli or bronchi of the lung. Some of them showed compression at the margin, while the progress of epithelium became papillary or multilayered with distortion of the pulmonary architecture (Fig. 3). Moderate nuclear polymorphism and cellular atypia were observed, but no mitotic figures. Moreover, an eosinophilic, mucinous, amorphous exudate that was stained positively by the PAS method was present within these lesions, resembling alveolar proteinosis. In addition to these lesions, foci of moderate squamous cell metaplasia which had become a multifocal replacement of alveolar epithelium by squamous cells (Fig. 4) and severe squamous cell hyperplasia, where keratinization had occurred with distorting alveolar architecture or slight nuclear atypia (Fig. 5), developed in the InAs group alone.

In both the GaAs and As_2O_3 groups, foci of mild hyperplasia of alveolar or bronchiolar cells were observed in the region of the peribronchiolar alveoli and alveolar ducts. Hyperplastic cells became single layered showing normal bronchiolo-alveolar architecture, and the margin of this lesion was not well defined.

In both the GaAs and InAs groups, there was moderate to severe lymphoid hyperplasia with particle deposition in the bronchial and mediastinal lymph nodes.

Histopathology of other organs

Slight to mild progressive lesions were obser-

Table 1 Inflammatory changes in the lung of hamsters

Group	Pneumonitis	Exudation	Thickening of pleura	AMϕ accumulation	Fibrotic proliferation
GaAs	2+	+	+	+	+
InAs	3+	3+	3+	+	3+
As_2O_3	2+	±	±	±	±
Control	+	−	−	±	−

The severity of the lung lesions was evaluated according to five grades
−, negative; ±, slight; +, mild; 2+, moderate; 3+, severe

Table 2 Hyperplastic lesions of alveolar or bronchiolar cells in the lung of hamsters

Group	Alveolar or bronchiolar cell hyperplasia	Alveolar or bronchiolar cell hyperplasia with squamous cell metaplasia	Squamous cell hyperplasia (keratinizing)	Squamous cell metaplasia (keratinizing)
GaAs	+	−	−	−
InAs	3+	−~3+	−~3+	−~3+
As_2O_3	2+	−	−	−
Control	−	−	−	−

The severity of the lung lesions was evaluated according to five grades
−, negative; ±, slight; +, mild; 2+, moderate; 3+, severe

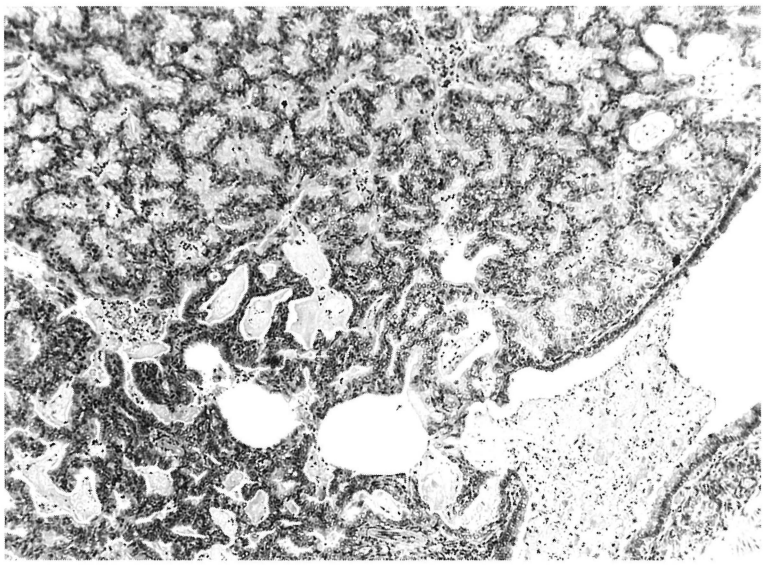

Fig. 3 Hyperplasia of alveolar or bronchiolar cells with squamous cell metaplasia of the lung and slight compression of the surrounding alveolar parenchyma in the InAs group. H. E. stain ×140.

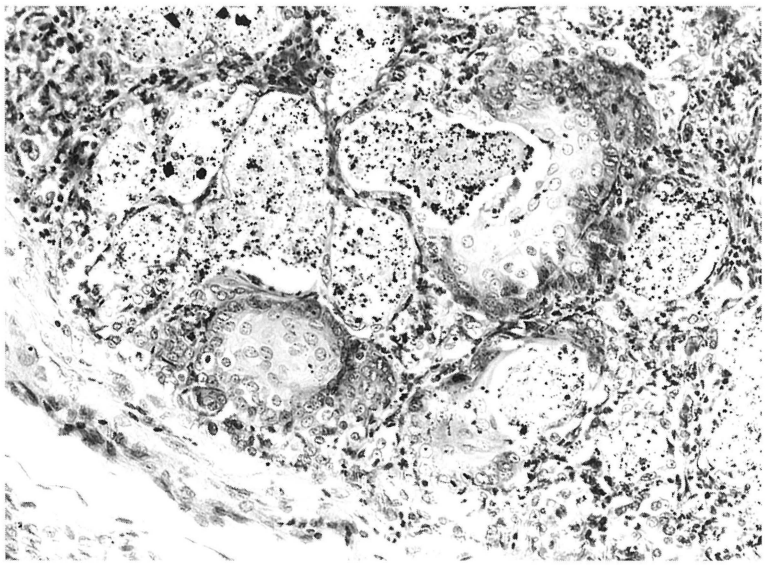

Fig. 4 Squamous cell metaplasia of the alveolar epithelium in the InAs group. H. E. stain ×280.

ved in the convoluted tubules of the kidney in both the GaAs and InAs groups. Degenerative change or atrophy of the epithelium in the convoluted tubules was noted in these groups. Furthermore, tubular necrosis, necrotic debris or hyaline casts in the convoluted tubules of the cortex and medulla were evident in the InAs group only. There were no such remarkable changes to the kidney in either the As_2O_3 or control groups. In contrast, the glomeruli

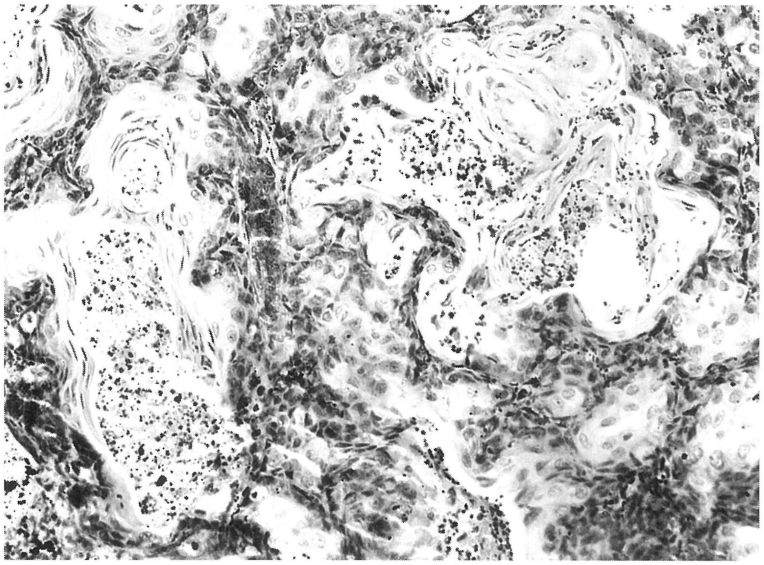

Fig. 5 Squamous cell hyperplasia with keratinization of the lung in the InAs group. H. E. stain ×280.

appeared normal and interstitial inflammatory cell infiltration was not observed. The severity of the pathological lesions in the kidney of the InAs-treated hamsters was greater than that in GaAs-treated hamsters.

Slight vacuolar degeneration of the hepatic cytoplasm was observed in the centrilobular region of the liver in all the groups. No marked changes were observed in any other organ in any of the groups.

Discussion

We evaluated the comparative toxic potency between GaAs, InAs and As_2O_3 particles when instilled intratracheally into hamsters for about 8 weeks. The results of this study clearly demonstrated the pulmonary, renal or systemic toxicity of InAs particles. Noticeable lesions of the lung comprised severe hyperplastic lesions observed among the InAs-treated hamsters. In particular, alveolar or bronchiolar cell hyperplasia with squamous cell metaplasia, squamous cell hyperplasia or squamous cell metaplasia with keratinization may be correlated to the overload condition induced by a large amount of low-solubility particles (i. e., titanium dioxide, diesel soot, carbon black, and talc). Carlton[1] mentioned that proliferative keratin cysts have been observed in the lung of Sprague-Dawley rats following chronic inhalation exposure to high concentrations of titanium dioxide (TiO_2) powder or Kevlar para-aramid fibrils. Furthermore, Watson and Valberg[28] mentioned that among laboratory animals, the rat has a unique sensitivity in its tumorigenic response to inhaled inert, insoluble particles when chronically exposed to high concentrations of these particles. In this study, hyperplastic lesions became evident following relatively short-term exposure to InAs particles (8 weeks) in hamsters. It is thus necessary to clarify species specificity and observation periods regarding particle-induced lung tumorigenicity. In addition to hyperplastic lesions, proteinosis-like lesions were found accompanying these lesions. In our previous study[25], we

recognized the appearance of pulmonary proteinosis-like lesions which were induced by exposure to InAs or InP particles. Friemann et al.[7] mentioned that alveolar proteinosis with proliferation of alveolar cell type II caused by quartz dust exposure might predictably be a precondition for tumor manifestation. It was reconfirmed that pathological change bearing a resemblance to alveolar proteinosis was produced by the instillation of InAs particles. Although we could not observe cellular or nuclear atypia, mitotic figures or invasive growth in these regions in the present study, the appearance of proteinosis-like changes and hyperplastic lesions including squamous cell metaplasia or squamous cell hyperplasia could possibly be a prerequisite for tumor development.

Histopathologic findings revealed that aggregates of particle-laden, degenerative or necrotic macrophages were detected in hamsters instilled with GaAs or InAs particles. Since macrophages play an important role in cleaning particles from the lung, an increase in the pulmonary persistence of GaAs or InAs particles may be due to their effects on this cell type. Tow kinds of cytokines, TNF-α and IL-1b, produced by pulmonary cells, predominantly by the alveolar macrophages, participate in numerous inflammatory processes, such as the recruitment and activation of neutrophils and lymphocytes, the stimulation of fibroblast proliferation and collagen synthesis, and increased oxygen radical production[2)3)24)25)]. Thus, it is likely that the presence of these two cytokines in the lung may contribute to the inflammatory response associated with exposure to certain environmental and occupational dusts. The increased pulmonary persistence and the presence of these inflammatory cytokines within the BALF may help to explain the increases observed in lung injury and inflammation caused by GaAs or InAs particles.

Morgan et al.[13)14)] reported that pulmonary toxicity of copper indium diselenide was more severe than that of copper gallium diselenide in rats, and that this was probably due to differences in the toxicities between indium and gallium. The results of our present study are practically consistent with their findings regarding the toxic manifestation of GaAs or InAs particles. Although each instillation dose of GaAs or InAs particles was almost the same (7.7 mg/kg), the total received dosage of GaAs particles (total dose: 16.2-20.3 mg/animal, 16 instillations) was much greater than that of InAs (total dose: 14.1-16.3 mg/animal, 14 instillations). GaAs or InAs particles were slightly soluble in in vitro or in vivo conditions, and each element was released partially from these particles[22)29)34)35)]. Similarly, Hirata et al.[9)], reported that in fact GaAs or InAs particles did dissolve to some degree and that the serum molar concentration of arsenic in the As_2O_3 group was higher compared with that in the GaAs or InAs group. Moreover, the serum molar concentration of gallium or indium was 32 times or 57 times higher than that of arsenic in the GaAs- or InAs- treated hamsters, while that of gallium or indium was almost the same level in both groups. However, the severity of pulmonary or systemic lesions in the As_2O_3 group was minimum among the treated groups. Accordingly, it would seem that gallium or indium was more potent than the arsenic released from GaAs or InAs particles. The difference in the toxic manifestation of the lung between the GaAs and InAs particles was probably due to the dissolved gallium or indium. We have already reported the testicular toxicity of GaAs or InAs particles by repetitive intratracheal instillations to rats or hamsters using the same

particle samples as used in this study[17)~19)]. Although GaAs, InAs and As_2O_3 particles caused a prominent increase in the relative lung weights, reflecting inflammatory response and increases in connective tissue, the weights of the liver in these 3 groups were significantly decreased compared with that in the control group. The weights of the kidney and spleen were significantly increased in the InAs group only. The pathological lesions in the kidney of InAs-treated hamsters were more severe than those in the GaAs-treated hamsters. Although remarkable pathological lesions were not recognized in the spleen, the InAs particles caused greater damage to the kidney and spleen, these being organs which were distant from the instillation site, as well as the lung than that coused by GaAs particles. These findings would seem to relate to dissolved indium rather than the InAs particles themselves, and the toxic effect of indium was more potent than that of gallium. Although no remarkable pathological changes to the liver were found, we were unable to clarify why the liver weights had diminished. It is possible that this finding may be some indicator of the biological effects of these three compounds.

In conclusion, InAs produces greater pulmonary, renal or systemic effects than GaAs or As_2O_3 particles when instilled intratracheally into hamsters. Additional animal studies, focusing on long-term observations are required to confirm whether pulmonary hyperplastic lesions with keratinization induced by InAs treatment are tumorigenic changes or not. We strongly feel that it is necessary to pay much greater attention to the exposure of humans to InAs particles.

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(和文抄録)

ガリウムヒ素，インジウムヒ素，三酸化ヒ素のハムスターを用いた気管内曝露による毒性の比較検討

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化合物半導体として用いられるガリウムヒ素(GaAs)，インジウムヒ素(InAs)と無機ヒ素化合物である三酸化ヒ素(As_2O_3)をハムスターの気管内に反復投与を行い，毒性の比較検討を行った．

12週齢の雄性シリアンゴールデンハムスターを用い，GaAs（1回投与量：7.7 mg/kg）とAs_2O_3（1.3 mg/kg）は週2回合計16回，InAs（7.7 mg/kg）は合計14回，各被験物質をリン酸緩衝液に懸濁し，気管内に投与した．対照群はリン酸緩衝液(1 ml/kg)のみを投与した．最終投与日の翌日に全例安楽死させ，剖検後，常法により病理標本を作製し，肺を中心とした病理組織学的検索を行った．投与期間中，InAs群では著明に体重が減少したが，GaAs群，As_2O_3群では対照群に比べて有意な差は認められなかった．肺においては，各群で肺炎が観察され，特にInAs群では好中球やマクロファージの集積，滲出液の貯留，胸膜の肥厚，線維組織の増生などの炎症性変化が重度に発現した．InAs群の全てのハムスターで，一部に角化した扁平上皮化生を伴う肺胞および細気管支上皮の増生が広範に認められた．さらに，InAs群の一部のハムスターで扁平上皮化生や扁平上皮の増生が観察されたが，GaAs群やAs_2O_3群ではこれらの変化は明らかではなかった．また，GaAs群とInAs群では腎臓の曲尿細管の軽度の障害が発現した．

以上の結果より，気管内に投与した場合，InAsの毒性はGaAsよりも強く発現し，As_2O_3は最も軽微であった．さらに，InAsは肺，腎臓や全身性に顕著に影響を及ぼすことが明らかになった．特に，肺においてはInAsは前がん病変を引き起こすことが示唆された．