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Review

Toxicity of Silicon Compounds in Semiconductor Industries

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Abstract: Toxicity of Silicon Compounds in Semiconductor Industries: Hiroshi NAKASHIMA, *et al.* Department of Preventive Medicine and Public Health, School of Medicine, Keio University—The toxicities of silane (SiH_4), tetraethoxysilane ($Si(OC_2H_5)_4$, TEOS) and dichlorosilane (SiH_2Cl_2, DCS) were reviewed in order to compare the toxicological properties of silicon compounds used in the semiconductor industry. Silane and TEOS showed similar toxicities, characterized by nephrotoxicity. Mice subjected to silane (2500, 5000 and 10000 ppm) or TEOS (1000 ppm) acute exposure developed acute tubular necrosis. Tubulo-interstitial nephritis was seen in mice which were subjected to an acute inhalation study and survived 2 wk of the observation period or those subjected to subacute inhalation studies of TEOS (100 and 200 ppm for 2 or 4 wk). Silane and TEOS, however, differed in the concentration at which they showed signs of toxicity. This may be due to their solubility in water and other metabolic factors, but their metabolic pathways have not yet been elucidated. TEOS injured nasal mucosa (1000 ppm for 2 h or more and 50, 100 and 200 ppm for 2 or 4 wk). It was observed at a lower concentration than nephrotoxicity in the 50 and 100 ppm subacute inhalation study. On the other hand, silane caused nasal mucosal lesions only at 5000 or 10000 ppm for acute inhalation, and those of subacute inhalation were mild (1000 ppm for 2 or 4 wk). DCS showed another type of adverse effect. It was an irritant and/or a corrosive agent to the respiratory tract in the acute (64 ppm for 1, 2, 4 or 8 h) and subacute (32 ppm for 2 or 4 wk) inhalation study. The fate of DCS in air was also studied and it was shown to form small particles including silicon and chlorine (Cl) atoms. Cl seems to play an important role in the toxicity of DCS.
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Silicon semiconductors are major products in the semiconductor industry. They are composed of silicon (Si) and small amounts of contaminants such as phosphorus (P) and boron (B). Major silicon compounds used in the semiconductor industry are silane, tetraethoxysilane (TEOS) and dichlorosilane (DCS). Some of adverse effects of these compounds were already known, but many things were yet to be elucidated 10 years ago. However, now we are able to have access to toxicological data on the materials used in the semiconductor industry. In this paper similarities and differences between these compounds are discussed based on the results of animal experiments.

Silane [CAS 7803-60-5] SiH_4

Silane is a colorless transparent gas at room temperature (molecular weight: 32.1, specific gravity: 1.114 (at 1 atm and 20°C), boiling point: − 111.8 or 9°C, melting point: −185°C)[1, 2]. Silane is odorless when highly diffused, but highly noxious in a concentrated state. Under normal conditions, silane is water-insoluble and does not react with water. In the presence of a concentrated acid or an alkali, it hydrolyzes into silicic acid and hydrogen. Silane reacts explosively with halogen gases. Silane is spontaneously flammable at room temperature, forming white smoke or yellow flakes of silicon oxide compounds. Its lowest concentration for explosion is 1.37 vol % under normal temperature and pressure. In the silicon semiconductor industry, silane is used to form silicon single crystals, epitaxial layer, polysilicon layer, silicon nitride layer and silicon oxide layer. It also serves to form the amorphous silicon layer for solar cells and photo-sensitive drums, ceramics and glass materials for optical fibers. Among the specialty gases used to produce semiconductors, silane consumption was the largest.

Male ICR mice (SPF grade) were exposed to 1000 ppm silane, a concentration 200 or 2000 times higher than the

recommended occupational exposure limits by many countries and academic associations, for 1, 2, 4 or 8 h (acute inhalation study) and for 6 h a day, 5 days per wk over 2 or 4 wk (subacute inhalation study)[3]. All mice in both studies survived to be sacrificed. In the acute inhalation study, no exposure-related changes were found in the hematological, biochemical or histopathological examinations. In the subacute inhalation study, hematological and biochemical examinations again failed to reveal any exposure-related changes. But mild irritation, manifested in the form of a small amount of exudate (8 of 10 mice), and inflammatory cells and/or necrotic cells on the nasal mucosa (6 of 10 animals) were observed only in the mice exposed to silane for 4 wk.

For acute toxicity at higher concentrations, male ICR mice were exposed to silane for 30 min (n=8), 1 or 4 h (n=12) at concentrations of 2500, 5000, 7500 (30 min experiment only) or 10000 ppm[4]. For groups including twelve mice, eight of twelve mice were selected for a 2-wk observation group, and the remaining four included in the 1- and 4-h exposure groups were put into the 2-d observation group. Six of the eight mice (2-wk observation group) in the 10000 ppm for 4 h exposure group died within 24 h after exposure. No deaths were observed in any of the other groups. A histopathological examination of the 2-d observation groups revealed acute tubular necrosis (ATN) of the kidney in the 10000 ppm for 1-h exposure group and the 2500, 5000 or 10000 ppm for 4-h exposure groups (Table 1). In addition, body weight loss, increased relative kidney weight, and increased BUN were also observed. Inflammatory changes in the nasal mucosa were observed at 5000 or 10000 ppm. Cytolysis in the red and the white pulp of the spleen was also seen. Tubulo-interstitial nephritis (TIN) of the kidney was observed in the 2-wk observation groups exposed to 7500 or 10000 ppm for 30 min and exposed to 5000 or 10000 ppm for one or 4 h (Table 1). The BUN levels in TIN-positive mice in the 1- and 4-h exposure groups were significantly higher than those in TIN-negative mice (data not shown).

Table 1. Results of high concentration silane exposure

	BUN (mg/m*l*)			Nasal Cavity	Kidney		Spleen	Bone Marrow	Thymus
	n	mean	SD		ATN	TIN	CRWP		
30 min exposure									
Control	5	24.3	2.6	0/5	–	0/5	0/5	n.d.	n.d.
2500 ppm	8	23.9	2.7	0/8	–	0/8	0/8	n.d.	n.d.
5000 ppm	8	23.4	2.6	0/8	–	0/8	0/8	n.d.	n.d.
7500 ppm	8	23.3	3.5	0/8	–	4/8	0/8	n.d.	n.d.
10000 ppm	8	21.1	5.4	0/8	–	6/8	0/8	n.d.	n.d.
1 h exposure									
Control	4	20.0	2.4	0/4	0/4	–	0/4	0/4	0/4
	8	20.4	2.7	0/8	–	0/8	0/8	0/8	0/4
2500 ppm	4	20.3	2.3	0/4	0/4	–	0/4	0/4	0/1
	8	21.6	3.4	0/7	–	0/7	0/7	0/7	0/5
5000 ppm	4	16.3	2.2	1/4	0/4	–	0/4	0/4	0/2
	8	22.3	1.0	0/8	–	1/8	0/8	0/8	0/5
10000 ppm	4	21.1	6.4	0/4	2/4	–	0/4	0/4	0/4
	8	25.4	3.5*	1/8	–	7/8	0/8	0/8	0/8
4 h exposure									
Control	4	23.2	2.4	0/4	0/4	–	0/4	0/4	0/2
	8	20.7	2.2	0/8	–	0/8	0/8	0/8	0/5
2500 ppm	4	17.5	2.2*	0/4	1/4	–	0/4	0/3	0/2
	8	21.8	6.0	0/8	–	0/8	0/8	0/8	0/3
5000 ppm	4	21.0	1.9	0/4	1/4	–	0/4	0/4	0/3
	8	24.6	3.9*	0/8	–	2/8	0/8	0/8	0/5
10000 ppm	1	51.8	–	1/1	1/1	–	1/1	0/1	0/1
	2	25.6	4.2*	0/2	–	1/2	0/2	0/2	0/1
	All of dead mice			7/9	9/9	–	8/9	6/8	9/9

*: $p<0.05$, Nasal Cavity: inflammatory changes in the nasal cavity. ATN: acute tubular necrosis, TIN: tubulo-interstitial nephritis. CRWP: cytolysis in the red and the white pulp. Bone Marrow: cytolysis of the hematopoietic cells, Thymus: cytolysis of lymphocytes. Upper row: 2-d observation, lower row: 2-wk observation. Mice exposed for 30 min were all observed for 2 wk.

Tetraethoxysilane (TEOS) [CAS No. 78-10-4] $Si(OC_2H_5)_4$

At room temperature, tetraethoxysilane (TEOS) is a colorless, transparent liquid with an ethanol-like smell (molecular weight: 101.01, liquid density: 1.22 kg/cm^3 (at 7°C), melting point: −127.0°C, boiling point: 31.8°C (at 1 atm), viscosity: 0.307cP (at 1 atm and 7°C))[5]. It is flammable when in contact with heat or flames. The odor threshold for men is 85 ppm, and mild irritation of the eyes and nose occurs at 250 to 700 ppm, and TEOS is claimed to have a lacrimation-inducing effect at 1200 ppm. In our experience, however, those with a keen sense of smell may detect the odor of TEOS at concentrations around 5 ppm. In the semiconductor industry, TEOS is used to form very thin- and equal-thickness silicon oxide layers, which is essential for manufacturing large and very large scale integrated circuits (LSI and VLSI).

Several reports on TEOS toxicity were published in the 1930s–50s. In recent years, high-purity TEOS has been introduced into the semiconductor industry, and the toxicity of high-purity TEOS was reevaluated. Male ICR mice (10/each group) were exposed to 1000 ppm TEOS for one, two, four or eight hours for an acute exposure experiment[6]. For a subacute experiment, mice (10/each group) were exposed to 200 ppm TEOS for six hours a day, 5 d a week over two or four weeks[6]. In the acute exposure experiment, one, one and six of the ten mice died in two-, four- and eight-hour exposure groups during the 2-wk observation period, respectively. None of those in the subacute exposure experiment died. ATN and cytolysis in the red and the white pulp of the spleen were again observed in mice which died during the acute inhalation study (Table 2). In addition, high prevalences of TIN were observed among the survivors in the acute inhalation study and mice in the subacute inhalation (Tables 2 and 3). An adverse effect on the respiratory system was also observed. Injury to olfactory epithelium was dominant for TEOS acute inhalation. Mice which died in the acute inhalation study developed necrosis of

Table 2. Results of TEOS 1000 ppm acute exposure

	BUN (mg/d*l*)			Creatinine (mg/d*l*)			Nasal cavity			Kidney		Spleen
	n	mean	SD	n	Mean	SD	Nac	Exu	Met	ATN	TIN	CRWP
Control	10	14.3	2.2	10	0.4	0.3	–	0/10	0/10	–	0/10	–
1 h	10	14.6	2.8	10	0.5	0.2	–	0/10	0/10	–	7/10	–
2 h	9	13.4	3.6	9	0.6	0.1	–	2/9	0/9	–	7/9	–
4 h	9	14.6	5.6	9	0.5	0.1	(1/1)	5/9	3/9	(1/1)	7/9	(1/1)
8 h	4	12.6	3.9	4	0.7	0.2*	(6/6)	3/4	2/4	(6/6)	4/4	(6/6)

*: $p<0.05$, ( ): positive mice/dead mice. Nec: necrosis of the olfactory epithelium. Exu: exudate containing inflammatory and necrotic cells. Met: respiratory epithelial metaplasia of the olfactory epithelium. ATN: acute tubular necrosis, TIN: tubulo-interstitial nephritis. CRWP: cytolysis in the red and white pulp.

Table 3. Results of TEOS 200 ppm subacute exposure

	BUN (mg/d*l*)			Creatinine (mg/d*l*)			Nasal cavity			Kidney
	n	mean	SD	n	mean	SD	Exu	SIN	Eo	TIN
2-wk exposure/2-d observation										
Control	5	12.6	0.8	5	0.7	0.1	0/5	0/5	0/5	0/5
Exposure	5	8.4	0.8**	5	0.8	0.1	4/5	5/5	5/5	4/5
2-wk exposure/2-wk observation										
Control	5	12.9	1.4	5	0.6	0.1	0/5	0/5	0/5	0/5
Exposure	5	11.5	1.7	5	0.8	0.1	0/5	0/5	5/5	4/5
4-wk exposure/2-d observation										
Control	5	13.4	2.2	5	0.7	0.1	0/5	0/5	0/5	0/5
Exposure	5	10.6	3.6	5	0.7	0.1	3/5	5/5	5/5	5/5
4-wk exposure/2-wk observation										
Control	5	12.0	1.1	5	0.6	0.1	0/5	0/5	0/5	0/5
Exposure	5	11.2	1.1	5	0.7	0.0**	0/5	3/5	5/5	4/5

**: $p<0.01$, Exu: exudate containing inflammatory and necrotic cells, SIN: submucosal infiltration of neutrophilic leukocytes, Eo: eosinophilic droplets in the nasal mucosa. TIN: tubulo-interstitial nephritis.

the olfactory epithelium of the nose, and inflammatory cell infiltration in the nasal mucosa was observed in mice subjected to the subacute inhalation study.

A further subacute inhalation experiment was done, focusing on toxicity at lower concentrations[7]. Mice were exposed to 50 or 100 ppm TEOS for 2 or 4 wk. Mild renal lesions were observed for a small number of mice exposed to 100 ppm TEOS (Table 4). No renal changes were observed at 50 ppm, but nasal mucosal lesions were frequently observed even in mice exposed to 50 ppm for 2 wk.

Dichlorosilane [CAS 4109-96-0] SiH_2Cl_2

At room temperature and increasing pressure, dichlorosilane becomes a colorless, transparent liquid[8]. Its explosive lower and upper limits are 4.1 and 98.8 vol%. DCS reacts violently with water to form hydrogen chloride. It also reacts violently with alkaline substances, generating heat. DCS is a material used to form polysilicon layers and epitaxial silicon layers. The estimated consumption of DCS was the second largest among specialty gases.

The fate of DCS in air was studied as well as its acute and subacute inhalation toxicities[9]. When blown out into the air, DCS decomposes regardless of the humidity, forming fine particles. Most of these particles are 0.1 μ meter or less in diameter and energy dispersive X-ray microanalysis revealed that these particles contain Silicon (Si) and Chlorine (Cl) atoms.

The LC_{50} value for 4-h DCS exposure was studied with male ICR mice and was calculated to be 144 ppm[9]. In the acute exposure experiment (64 ppm for 1, 2, 4 or 8 h), no exposure-related changes were found in the hematological and biochemical examination. Histopathological examination, however, revealed epithelial lesions in the nasal mucosa and the trachea in all of the exposure groups, and this can be attributed to irritating or corrosive effects of DCS (Table 5). Moreover,

Table 4. Results of TEOS 50 and 100 ppm subacute exposure

	BUN (mg/d*l*)			Creatinine (mg/d*l*)			Nasal cavity		Kidney
	n	Mean	SD	N	Mean	SD	SIN	APF	TIN
2-wk exposure									
Control	10	21.1	3.5	10	0.3	0.1	0/10	0/10	0/10
50 ppm	10	22.4	4.1	10	0.3	0.1	7/10	9/10	0/10
100 ppm	10	18.9	3.1	10	0.3	0.1	10/10	10/10	2/10
4-wk exposure									
Control	10	32.3	6.7	10	0.3	0.1	0/10	0/10	0/10
50 ppm	10	24.0	3.4	10	0.3	0.0	10/10	10/10	0/10
100 ppm	10	24.3	3.5	10	0.3	0.1	10/10	10/10	2/10

SIN: submucosal infiltration of neutrophilic leukocytes, APF: all positive findings include exudates in the nasal cavity, eosinophilic droplets in the nasal mucosa and SIN. TIN: tubulo-interstitial nephritis.

Table 5. Results of DCS acute and subacute inhalation study

	Acute exposure					2-wk exposure		4-wk exposure	
	Control	1 h	2 h	4 h	8 h	Control	Exposure	Control	Exposure
Nasal cavity									
Exu	0/10	9/10	10/10	10/10	10/10	0/10	10/10	2/10	10/10
NI	0/10	9/10	10/10	10/10	10/10	0/10	10/10	0/10	10/10
IRE	0/10	10/10	10/10	10/10	10/10	0/10	10/10	0/10	10/10
IOE	0/10	0/10	8/10	8/10	5/10	0/10	10/10	0/10	7/10
Trachea									
ENEC	0/10	5/10	5/10	10/10	10/10	–	–	–	–
DCLSEC	0/10	10/10	10/10	10/10	10/10	–	–	–	–
RHSM	–	–	–	–	–	0/10	10/10	0/10	9/9

Exu: exudate, NI: necrotic and inflammatory cells, IRE: injury to the respiratory epithelium, IOE: injury to the olfactory epithelium. ENEC: enlarged nuclei of epithelial cells, DCLSEC: disturbed cell layer of structure of epithelial cells, RHSM: reverse cell hyperplasia and/or squamous metaplasia.

for groups exposed for 2 h or more, mice showed weight loss and respiratory manifestation including wheezing and piloerection.

Mice exposed to 32 ppm DCS for 2 or 4 wk also exhibited depression of body weight gain, wheezing and piloerection. They also had epithelial lesions in the nasal mucosa and the trachea (Table 5). Some of the mice exposed to DCS for 2 or 4 wk developed squamous metaplasia of the nasal mucosa and the trachea.

Discussion

When mice were subjected to acute inhalation exposure to silane, concentrations of 1000 ppm (4-h exposure), 2500 ppm (1-h exposure) or 5000 ppm (30-min exposure) did not produce any effect. In the past, silane was regarded as a highly toxic and strongly irritative gas, but the above findings show that its toxicity and irritant effects are not so severe as formerly believed.

Through recent studies on TEOS[6, 7], its nephrotoxicity was reconfirmed. Rowe *et al.*[10] reported that increased renal weight was noted after five to ten exposures, and after 30 exposures mild to moderate renal damage was observed, when rats were exposed to 125 ppm TEOS for seven hours. Pozzani and Carpenter[12] exposed guinea pigs, rats and mice to 88, 50 or 23 ppm of TEOS for seven hours a day, five days a week, for 90 days. They stated that the findings for the kidneys were unremarkable, except for a decrease in the kidney weight of the mice in the 88 ppm exposure group. The lowest limit of nephrotoxicity was between 50 and 100 ppm in the subacute inhalation study[4], which was compatible with previous reports.

In reports published in the 1930s–1950s[10–13], the lung and liver were also injured as well as the kidney, but recent studies showed that the kidney and the nasal mucosa were target sites. No suitable interpretation explaining the discrepancy could be given, but the purity of TEOS or animal conditions may be some of the reasons.

Silane and TEOS showed similar toxicities, characterized by nephrotoxicity. Mice subjected to silane or TEOS acute exposure (2500, 5000, and 10000 ppm for silane and 1000 ppm for TEOS) developed ATN, and TIN was seen in mice survived the 2 wk observation period or those used for subacute inhalation studies of TEOS (100 and 200 ppm for 2 or 4 wk). Moreover, intraperitoneal injection of 1000 mg/kg of tetramethoxysilane [$Si(OCH_3)_4$, TMOS], another type of silicon alkoxide, was shown to cause ATN[14].

From our results, silane or its metabolite are presumed to be excreted from the kidney. As for TEOS, the exposure-related increase in the silicon concentration in blood has been reported for mice treated with TEOS[15]. The Si atom was also detected in the deposits on the damaged renal tubule membrane in mice given TEOS[16]. Although the chemical formula has not yet been identified, these results suggest that inhaled TEOS is metabolized to form unidentified silicon compound(s) and excreted from the kidney. Silicic acid is a known form of Si in blood, and polymerized metasilicic acid is reported to cause ATN[17]. Silane and TEOS might be metabolized to silicic acid or other common metabolites. The metabolized silicon compound is presumed to exhibit injury to renal tubules when it is excreted from the kidney.

Silane and TEOS, however, differed in the concentration at which they showed nephrotoxicity. This may be due to their solubility in water or other chemical properties, but their metabolic pathway has not yet been elucidated.

Cytolysis in the red and the white pulp of the spleen was a common finding for silane and TEOS. The same type of lesion was observed in the bone marrow or thymus of mice treated with silane. The spleen of mice treated with TMOS also had the same lesion[14]. Lympholysis is seen in the administration of alkylating agents and others, and cytolysis of hematopoetic cells is observed during therapy for leukemia. Arashidani *et al.*[18] reported positive results of SCE for TEOS or TMOS. Although we can not exclude the possibility of a secondary reaction, the reported histopathological lesion may be the result of injury to DNA caused by silane or TEOS.

In an acute inhalation study of DCS[19], irritation to the eye and the respiratory symptom were seen in rats exposed to 257 ppm or higher concentrations. The gross pathological finding includes the accumulation of effusion in the pleural cavity and the trachea. Nine times exposure of 3 to 15 ppm DCS (6 h/d) to rats revealed irritation of the eyes and respiratory organs including squamous epithelialization of the upper respiratory tract[20]. In our study, DCS was an irritant and/or a corrosive agent to the respiratory tract, which reconfirmed previous reports.

Hydrogen chloride (HCl) is produced by hydrolysis of DCS, and exposure to HCl was also conducted for positive control[20]. Toxicity of HCl was small, however, and the authors stated that other reactive intermediates produced by the hydrolysis of DCS may be involved. It is suggested that the fine particle containing Cl, or HCl adhering to the particles and its transportation to the lower respiratory tract might play a significant role in the respiratory toxicity of DCS as well as HCl vapor[9].

TEOS also appeared to have a toxic effect on the nasal mucosa, and this was seen at the lower concentration than nephrotoxicity. On the other hand, the nasal mucosal lesion caused by 1000 ppm silane inhalation was minimal. On the inhalation toxicity of TMOS, Koleser *et al.*[21] reported injury to the eye in addition to the respiratory tract at lower concentrations than 50 ppm. They were seen at different concentrations and their character was also different. The side chains of silicon compounds might play some roles in mucosal injury.

In mice, the LC_{50} for four-hour exposure to silane was 9600 ppm[22]. According to Takebayashi[4], it was 5000–10000 ppm and the LC_{50} for 30-min or 1 h exposure was at least 10000 ppm. The LC_{50} for DCS 1-h exposure in rats is 314 ppm, and the four-hour exposure LC_{50} in mice is 144 ppm[9]. These data were comparable with each other. ATN is thought to play an important role in death caused by silane or TEOS. But the cause of death is yet to be elucidated for DCS.

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