THE RESULTS OF MICROBIAL MUTATION TEST FOR FORTY-THREE INDUSTRIAL CHEMICALS

Hidesuke SHIMIZU,* Yuji SUZUKI,* Nozomi TAKEMURA,*
Sumio GOTO** and Hidetsuru MATSUSHITA**

工業化学物質 43 種類の突然変異原性について

清水英佑*, 鈴木勇司*, 竹村 望*
後藤純雄**, 松下秀鶴**

The mutagenicity of 43 industrial chemicals in *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2uvrA) was examined. The output of these chemicals in Japan is more than a million kilograms per year. The mutation test was carried out under the condition of absence and presence of rat microsomal activation.

Two chemicals, hexamethylenetetramine and 4,4'-methylenediphenyldiisocyanate, showed mutagenic activity in *S. typhimurium* TA98 and TA100 by metabolic activation. Hexamethylenetetramine also showed mutagenic activity in TA98 without microsomal activation.

No mutagenic activity was observed in the 41 chemicals including 4 volatile and gaseous compounds.

INTRODUCTION

A large number of industrial chemicals have been used as raw materials, organic solvents and intermediates in the production of food additives, drugs, cosmetics, plastics, etc.

Because of its rapidity and economic return, the *Salmonella*/mammalian microsome test developed in 1975 by Ames *et al.*¹⁾ is useful in the chemical industry for screening chemicals for their carcinogenic potential. The mutagenic activity of hundreds of chemicals has been examined by this test, and a close relationship between mutagenicity and carcinogenicity has been demonstrated.^{2,3)} We have tested the mutagenicity of 43 compounds produced as more than a million kilograms per year in Japan in order to estimate the carcinogenic

risk, and the results are reported herein. Workers in the chemical industry are being exposed to these chemicals, and mutagenicity and/or carcinogenicity of most of them have not been tested so far.

MATERIALS AND METHODS

Chemicals. The chemical names, structures, sources, diluents, CAS numbers and purity of the 43 chemicals tested are as shown in Tables 1 and 2. The annual output of the 43 chemicals is as shown in Table 3.

Strains. Five strains of *Salmonella typhimurium* (TA100, TA98, TA1535, TA1537 and TA1538) and a strain of *Escherichia coli* (WP2uvrA) were used for the mutagenicity test. The strains of *S. typhimurium* were kindly provided by B.N. Ames, U.S.A. and *E. coli* by M. Ishizawa, Japan.

S9 mix. The S9 fraction was prepared from the liver of male Sprague-Dawley rats, weighing about 220 g (seven weeks old), pretreated with polychlorinated biphenyl (KC 500) at a dose of 500 mg/kg body weight five days before sacrifice. The S9 mix contained 0.1 ml of S9/ml.

Mutation test. The mutagenicity of 39 com-

* Department of Public Health, The Jikei University School of Medicine

** The Institute of Public Health
Received for publication, July 13, 1985

* 東京慈恵会医科大学公衆衛生学教室

** 国立公衆衛生院

昭和60年7月13日受付

Table 1. List of 39 compounds tested for mutagenicity.

No.	Name (IUPAC)	Structure	Purity (%)	Diluent	Source	CAS No.	Muta-genicity	Carcino-genicity (Ref. No.)
1.	Aluminium fluoride	AlF_3	90	H_2O	W	7784-18-1	—	?
2.	3-Amino-6-chlorotoluene-4-sulfonic acid	$\text{C}_6\text{H}_4(\text{CH}_3)(\text{NH}_2)(\text{Cl})(\text{SO}_3\text{H})$	99.9	DMSO	T	88-53-9	—	?
3.	1-Amino-2-propanol	$\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{NH}_2$	97	H_2O	T	78-96-6	—	?
4.	Ammonium fluoride	NH_4F	95	H_2O	W	12125-01-8	—	?
5.	Ammonium peroxodisulfate	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	98	H_2O	W	7727-54-0	—	?
6.	Barium chloride	BaCl_2	99	H_2O	W	10361-37-2	—	?
7.	2-Butanone	$\text{CH}_3\text{COC}_2\text{H}_5$	99	H_2O	W	78-93-3	—	— (7)
8.	Butyl acetate	$\text{CH}_3\text{COOC}_4\text{H}_9$	99.6	DMSO	W	123-86-4	—	?
9.	Cerium(IV)dioxide	CeO_2	99.9	H_2O	W	1306-38-3	—	?
10.	Copper(I)oxide	Cu_2O	90	H_2O	W	1317-39-1	—	?
11.	Decanedioic acid	$\text{HOOC}(\text{CH}_2)_8\text{COOH}$	99	DMSO	T	111-20-6	—	?
12.	1-Dodecanol	$\text{C}_{12}\text{H}_{25}\text{OH}$	90	DMSO	W	112-53-8	—	— (35)
13.	Dodecylbenzen	$\text{C}_6\text{H}_5(\text{C}_{12}\text{H}_{25})$	98	DMSO	T	123-01-3	—	— (34)
14.	2-Ethyl-1-hexanol	$\text{CH}_3(\text{CH}_2)_3\text{CH}(\text{C}_2\text{H}_5)\text{CH}_2\text{OH}$	98	DMSO	W	104-76-7	—	?
15.	Ethylenebisoctadecanamide	$\text{C}_{17}\text{H}_{35}\text{CONHCH}_2\text{CH}_2\text{HNOCH}_{35}\text{C}_{17}$	99	DMSO	T	110-30-5	—	?
16.	2-Ethoxyethanol	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_4\text{OH}$	98	DMSO	W	110-80-5	—	— (7)
17.	Glycerol	$\text{C}_3\text{H}_8(\text{OH})_3$	99.6	H_2O	W	56-81-5	—	— (7, 9)
18.	Hexafluorosilicic acid	H_2SiF_6	40-45	H_2O	W	16961-83-4	—	?
19.	Hexamethylene tetramine	$(\text{CH}_2)_6\text{N}_4$	99.9	H_2O	W	100-97-0	+	+ (5-9)
20.	Hexanedioic acid	$\text{HOOC}(\text{CH}_2)_4\text{COOH}$	99	DMSO	T	124-04-9	—	?
21.	3-Hydroxy-2-naphthoic acid	$\text{HOC}_{10}\text{COOH}$	99.9	DMSO	T	92-70-6	—	?
22.	Iron(III)chloride	FeCl_3	99	H_2O	W	7705-08-0	—	— (7, 36)
23.	Isobutyl alcohol	$\text{C}_4\text{H}_9\text{OH}$	99.7	H_2O	W	78-83-1	—	+ (14, 15)
24.	Methanol	CH_3OH	99.6	H_2O	W	67-56-1	—	— (7, 24)
25.	Methyl acetoacetate	$\text{CH}_3\text{COCH}_2\text{COOCH}_3$	99	H_2O	T	105-45-3	—	?
26.	4,4'-Methylenedi-phenylisocyanate	$\text{CH}_2(\text{C}_6\text{H}_4\text{NCO})_2$	98	DMSO	T	101-68-8	+	?(12)
27.	4-Methyl-2-pentanol	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_3$	98	DMSO	T	108-11-2	—	?
28.	p-Nonylphenol	$\text{C}_6\text{H}_4(\text{C}_9\text{H}_{19})(\text{OH})$	89	DMSO	T	104-40-5	—	?
29.	Octadecanoic acid	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$	60	Acetone	W	57-11-4	—	— (7, 9, 15, 31)
30.	Oleic acid	$\text{C}_{17}\text{H}_{33}\text{COOH}$	99.9	DMSO	W	112-80-1	—	— (7, 9, 15, 30, 31)
31.	Pentaerythritol	$\text{C}(\text{CH}_2\text{OH})_4$	90	H_2O	W	115-77-5	—	?
32.	Pentasodium triphosphate	$\text{Na}_5\text{P}_3\text{O}_{10}$	90	H_2O	W	13573-18-7	—	?
33.	2-Propanol	$\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$	99	H_2O	W	67-63-0	—	+ (15-17)
34.	Sodium dithionite	$\text{Na}_2\text{S}_2\text{O}_4$	89.1	H_2O	W	7775-14-6	—	?
35.	Tetrafluoroboric acid	HBF_4	42	H_2O	W	16872-11-0	—	?
36.	Tetramethylenesulfone	$\text{C}_4\text{H}_8\text{SO}_2$	99	H_2O	T	126-33-0	—	?
37.	Trichloroisocyanuric acid	$\text{C}_3\text{Cl}_3\text{N}_3\text{O}_3$	97	H_2O	T	87-90-1	—	?
38.	Urea	H_2NCONH_2	99	H_2O	W	57-13-6	—	— (20)
39.	p-Xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	98	DMSO	W	106-42-3	—	?

T: Tokyo Kasei Kogyo Co. LTD. Tokyo, Japan. W: Wako Pure Chemical Industries, LTD., Osaka, Japan.

Table 2. List of 4 volatile compounds tested for mutagenicity.

No.	Name (IUPAC)	Structure	Purity (%)	Diluent	Source	CAS No.	Mutagenicity	Carcinogenicity
1.	Ammonia	NH ₃	99.9	Air	TAK	7664-41-7	—	— ⁹⁾
2.	Butane	C ₄ H ₁₀	99	Air	TAK	106-97-8	—	?
3.	2-Methylpropene	(CH ₃) ₂ C=CH ₂	99	Air	TAK	115-11-7	—	?
4.	Chlorine	Cl ₂	99.9	Air	TAK	7782-50-5	—	?

TAK: Takachiho Chemical Co. Tokyo, Japan.

pounds, excluding four volatile ones (ammonia, butane, chlorine and 2-methylpropene) was tested by the preincubation method⁴⁾ with S9 mix, which was slightly modified from the Ames test.¹⁾ When *E. coli* instead of *S. typhimurium* was used, histidine and biotin in the top agar were replaced by tryptophan at the same concentration. The 39 compounds tested were dissolved in sterilized diluents, as shown in Table 1, and 0.1 ml of bacterial strain and 0.5 ml of S9 mix or sodium phosphate buffer (pH 7.4) were added to a sterile test tube containing 0.1 ml of various concentrations of the chemicals. This mixture was preincubated in a shaker water bath at 37°C for 20 minutes, and then added to 2 ml of molten top agar (45°C). The contents of each tube were mixed and poured onto a minimal glucose agar plate immediately. The plates were incubated at 37°C for 48 hours, and then the number of revertant colonies on each plate was scored with an automated colony counter.

In the test of such gaseous or highly volatile compounds as ammonia, butane, chlorine and 2-methylpropane, a minimal glucose agar plate covered with 0.1 ml of one of the strains and 0.5 ml of S9 mix or buffer was placed upside down without a lid inside a glass chamber. This method has been described in detail elsewhere.⁵⁾

All these tests were performed in duplicate. 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), 9-aminoacridine (9AC), 4-nitroquinoline-1-oxide (4NQO), benzo(a)pyrene (B(a)P), 2-aminoanthracene (2AA) and 2-nitrofluorene (12NF) were used as positive control (see in Table 4).

A contamination test was carried out in each experiment. The background bacterial lawn was checked routinely by dissected microscope.

RESULTS AND DISCUSSION

The results of the mutagenicity of the 39 tested compounds, which were in crystal, powdered or liquid form, are shown in Table 1 and those of four highly volatile or gaseous compounds in Table 2. The details with regard to the mutagenicity of each compound are given in Tables 4 and 5.

Seven compounds—1-dodecane (DOD), chlorine (CH), oleic acid (OLE), 2-ethyl-1-hexanol (2HE), *p*-nonylphenol (NP), trichloroisocyanuric acid (TCI) and *p*-xylene (XY)—were toxic to the bacterial strains used for the test. DOD, CH and OLE were toxic at 50 µg/plate to *S. typhimurium*, and 2HE, NP, TCI and XY at 50 or 100 µg/plate to both *S. typhimurium* and *E. coli*.

Only two out of the 43 compounds—hexamethylenetetramine (HMT) and 4,4'-methylenediphenyldiisocyanate (MDI)—were mutagenic. The other 41 compounds presented no mutagenic activity either in the presence or absence of S9 mix. The mutagenicity of 11 out of the 43 compounds (25.6%) has already been reported by mutation tests including chromosomal aberration, sister chromatid exchange and dominant lethal tests. Thirty-two out of the 43 compounds (74.4%) had not been tested, nor have their mutagenicity been reported. Only 14 out of the 43 compounds (32.5%) have been tested for their carcinogenicity; carcinogenicity was detected in two chemicals and one manufacturing process of a chemical.

HMT was mutagenic to *S. typhimurium* TA100 with S9 mix and to TA98 with and without S9 mix. There was a weak dose-response correlation between the number of histidine revertant colonies (His⁺) of TA100 and the concentration of the chemical in the absence of S9 mix. The mutagenicity of the chemical has not been reported so far.

Table 3. The annual output in Japan of the 43 chemicals tested for mutagenicity (1,000 t/year).

No.	Chemicals (IUPAC)	1979	1981	1982	1983	1984
1.	Aluminium fluoride	61	61		45	45
2.	3-Amino-6-chlorotoluene-4-sulfonic acid	1	1		1	1
3.	1-Amino-2-propanol	1	1			1
4.	Ammonium fluoride	3	3			3
5.	Ammonium peroxodisulfate	4	4		3	3
6.	Barium chloride	10		9	9	11
7.	2-Butanone	88		97	102	111
8.	Butyl acetate	36		29	31	34
9.	Cerium(IV)dioxide	2	2		2	2
10.	Copper(I)oxide	4	4		6	4
11.	Decanedioic acid	2	2		2	1
12.	1-Dodecanol	78		76		
13.	Dodecylbenzene	200		157	180	
14.	2-Ethyl-1-hexanol	264		226	219	
15.	Ethylenebisoctadecanamide	4	4		4	1
16.	2-Ethoxyethanol	41		50	54	61
17.	Glycerol	70		77	72	71
18.	Hexafluorosilicic acid	2	2		2	2
19.	Hexamethylenetetramine	21		13	15	16
20.	Hexanedioic acid	47	47		47	47
21.	3-Hydroxy-2-naphthoic acid	3	3		2	1
22.	Iron(III)chloride	211		247	252	281
23.	Isobutyl alcohol	49		33	29	26
24.	Methanol	940		625	373	280
25.	Methyl acetoacetate	3	3		3	3
26.	4,4'-Methylenediphenyldiisocyanate	44		58	70	85
27.	4-Methyl-2-pentanol	3	3	3		3
28.	<i>p</i> -Nonylphenol	16	16	16		16
29.	Octadecanoic acid	26		23	8	8
30.	Oleic acid	10		16	15	16
31.	Pentaerythritol	40		31	32	30
32.	Pentasodium triphosphate	122		79	66	61
33.	2-Propanol	96		96	90	92
34.	Sodium dithionite	31		35	33	34
35.	Tetrafluoroboric acid	1	1		1	1
36.	Tetramethylenesulfone	1	1			
37.	Trichloroisocyanuric acid	10	10		10	10
38.	Urea	2,083		1,185	981	1,120
39.	<i>p</i> -Xylene	647		583	620	683
<hr/>						
1.	Ammonia	2,831		2,010	2,010	2,029
2.	Butane					
3.	2-Methylpropene(Butylene)	1,745		1,466	1,434	1,526
4.	Chlorine	2,700		2,471	3,265	2,748

IUPAC: International Union of Pure and Applied Chemistry.

Table 4. Mutagenic activities of 39 compounds.

No.	Compound	Dose μg/plate	Revertant colonies/plate									
			TA100	TA1535	WP 2 uvrA	TA98	TA1537	TA1538				
			-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
1. Aluminium fluoride												
	H ₂ O (control)	0.01	501±84.7	—	—	—	—	—	—	—	—	—
		0.05	—	—	—	1,082±293.7	278±64.8	—	—	—	—	—
	ENNG	5.0	—	1,101±683.1	—	—	—	—	—	—	—	—
	9AC	80.0	—	—	—	—	889±275.7	—	—	—	—	—
	4NQO	0.25	—	—	—	—	—	270±66.2	—	—	—	—
	B(a)P	5.0	1,084±236.3	—	—	—	809±108.4	313±41.6	—	354±89.4	—	—
	2AA	5.0	—	—	440±198.6	359±127.0	—	—	—	—	—	—
	1	144	165	38	20	39	42	30	37	16	15	18
	5	164	160	32	20	34	43	34	31	9	17	19
	10	149	169	40	19	42	45	32	40	16	21	19
	50	156	166	32	25	35	42	37	35	13	15	16
	100	161	174	30	18	38	46	32	35	12	20	26
	500	158	187	33	18	36	37	37	35	15	12	26
	1,000	154	184	39	20	28	48	41	42	17	13	19
	5,000	144	188	29	10	35	46	27	44	9	17	24
		122	137	34	14	21	23	38	49	9	12	36
		128	153	38	18	23	26	43	47	6	9	32
		142	141	38	14	29	19	51	46	11	19	28
		138	140	31	17	20	29	44	48	8	17	29
		136	129	22	19	25	28	48	55	9	21	32
		140	133	33	13	26	20	51	50	9	13	33
		138	141	35	17	19	28	50	55	11	16	20
		131	126	40	13	21	34	46	65	10	13	34
												51
2. 3-Amino-6-chlorotoluene-4-sulfonic acid												
	1	122	137	34	14	21	23	38	49	9	12	36
	5	128	153	38	18	23	26	43	47	6	9	32
	10	142	141	38	14	29	19	51	46	11	19	28
	50	138	140	31	17	20	29	44	48	8	17	29
	100	136	129	22	19	25	28	48	55	9	21	32
	500	140	133	33	13	26	20	51	50	9	13	33
	1,000	138	141	35	17	19	28	50	55	11	16	20
	5,000	131	126	40	13	21	34	46	65	10	13	34

3. 1-Amino-2-propanol		1	177	183	39	12	34	30	21	43	7	10	18	28
	5	160	187	41	14	14	35	34	18	36	8	14	18	24
	10	164	181	38	14	14	41	44	19	45	9	13	20	29
	50	167	183	36	18	18	33	37	22	37	9	13	23	28
	100	175	165	41	12	12	31	32	21	34	10	10	24	30
	500	144	189	38	18	18	34	37	16	34	8	19	21	24
	1,000	163	183	44	19	19	35	42	24	31	9	8	22	30
	5,000	94* ^c	106*	17*	18*	18*	36	37*	15*	26*	4*	12*	19	30
4. Ammonium fluoride		1	146	157	38	23	24	41	25	39	11	9	20	30
	5	134	140	33	13	13	26	35	27	37	14	17	20	31
	10	143	170	42	16	16	29	36	29	39	18	21	25	26
	50	140	173	40	14	14	33	38	26	39	15	18	21	33
	100	149	145	45	14	14	33	40	24	39	15	19	20	29
	500	160	146	43	13	13	35	39	25	42	16	22	23	31
	1,000	135	165	41	16	16	39	37	35	37	10	21	22	34
	5,000	136	182	28	11*	11*	39	37	35	42	17	16	15	36
5. Ammonium peroxodisulfate		1	150	143	31	17	32	32	25	27	16	17	19	32
	5	136	156	33	18	18	32	37	30	35	17	19	23	28
	10	172	152	41	21	21	34	39	28	35	15	16	18	28
	50	164	166	37	15	15	41	44	35	31	14	23	19	31
	100	172	147	41	16	16	37	42	36	33	13	17	27	30
	500	145	150	40	15	15	35	44	33	37	16	17	20	22
	1,000	166	159	27	17	17	36	32	30	42	17	16	24	22
	5,000	137	168	23	15	15	23	35	28	32	17	17	23	19
6. Barium chloride		5	131	152	36	20	23	33	26	37	23	30	18	22
	10	128	164	38	18	18	34	26	22	40	26	30	21	18
	50	133	163	32	18	18	27	32	28	41	26	33	18	26
	100	130	144	29	16	16	28	28	35	42	21	35	19	21
	500	131	144	29	16	16	19	34	31	42	20	33	17	18
	1,000	144	155	39	20	20	31	28	36	46	22	36	16	27
	5,000	0*	159	27	19	19	20	28	26	48	21	36	17	17

7. 2-Butanone	5	153	148	32	14	26	27	34	32	10	22	31	29
	10	135	155	29	12	29	27	41	45	13	14	27	28
	50	146	148	29	17	30	26	31	38	15	16	27	33
	100	144	136	27	18	32	27	32	37	17	16	24	23
	500	128	152	34	16	29	32	33	37	12	20	28	29
	1,000	138	148	31	13	29	28	40	39	17	28	31	30
	5,000	130	130	27	11	29	31	33	38	16	32	27	28
8. Butyl acetate	1	141	135	25	14	20	29	26	40	19	19	14	23
	5	138	135	26	14	21	31	23	49	15	26	26	24
	10	139	134	30	16	23	36	21	38	26	33	22	21
	50	141	147	31	13	29	36	30	43	11	17	18	25
	100	134	151	22	15	21	28	22	39	15	21	17	25
	500	146	146	24	14	26	30	30	30	17	24	17	19
	1,000	140	148	17*	14	23	24	0*	35	14	25	18	31
9. Cerium(IV) dioxide	5,000	0*	50*	0*	0*	0*	9*	0*	33*	0*	11*	0*	21*
	1	150	177	30	11	25	30	25	34	6	11	25	31
	5	160	192	30	17	24	31	27	36	5	15	34	40
	10	187	190	36	14	32	30	23	37	6	14	29	43
	50	169	186	34	19	25	25	21	29	10	12	23	50
	100	139	212	30	19	25	25	22	40	8	11	35	43
	500	156	206	35	14	26	26	19	35	10	12	23	41
10. Copper(I)oxide	1,000	168	199	37	14	25	25	28	33	12	17	35	38
	5,000	163	188	30*	10*	21	22	28	42	9*	12*	22	32
	1	132	141	31	12	42	60	33	39	17	16	21	31
	5	135	157	45	11	59	51	25	34	8	16	24	27
	10	144	137	29	10	49	54	24	33	10	17	24	25
	50	139	137	40	13	41	50	28	34	17	26	22	30
	100	149	133	35	15	48	54	24	26	12	15	21	28
	500	150	154	37	22	39	60	31	37	7	18	17	26
	1,000	156	173	39	21	32	38	39	37	7	7	16	24
	5,000	0*	0*	42	16	4*	32	0*	14*	0*	6*	0*	14*

11. Decanedioic acid	1	130	130	29	9	17	26	43	49	17	23	23	38
	5	119	138	34	11	24	22	52	50	13	25	26	38
	10	131	130	26	15	23	27	39	46	14	24	31	33
	50	125	123	34	13	18	24	47	56	11	24	27	33
	100	136	119	36	16	26	29	50	47	13	27	36	39
	500	140	122	28	13	24	32	42	56	11	18	20	36
	1,000	127	132	26	12	27	23	34	45	18	12	28	33
12. 1-Dodecanol	5,000	112	134	36	14	24	27	45	47	12	20	30	32
	0.01	—	—	33	35	—	—	—	—	10	21	21	27
	0.05	152	145	36	25	29	40	26	31	16	25	15	19
	0.1	139	158	39	34	22	42	29	25	16	25	24	21
	0.5	141	148	40	31	31	44	25	32	9	17	16	18
	1	161	153	39	24	36	36	25	38	13	29	16	25
	5	140	147	28	32	28	38	23	33	15	27	16	22
13. Dodecylbenzene	10	125	172	14*	34	34	41	19	37	8	17	13	20
	50	0*	163	0*	37	29	48	0*	32	4*	26	7*	21
	5	144	153	28	19	24	40	22	30	16	28	15	31
	10	133	142	24	16	19	27	25	28	19	31	17	29
	50	134	127	22	14	20	32	24	32	20	37	20	28
	100	135	138	21	16	23	35	22	24	22	28	26	29
	500	132	133	24	14	25	32	33	22	18	26	17	23
14. 2-Ethyl-1-hexanol	1,000	144	149	23	16	20	37	19	27	13	30	15	24
	5,000	139	149	36	14	26	31	23	44	14	30	18	26
	1	144	170	39	23	32	31	24	44	13	36	25	24
	5	166	171	23	19	30	26	33	61	11	28	33	30
	10	161	149	26	18	27	31	29	48	15	23	29	25
	50	155	147	33	13	26	33	28	57	16	30	25	30
	100	133	151	19	14	28	33	37	51	12	26	18	30
	500	0*	0*	0*	0*	0*	0*	0*	0*	12	39	0*	0*
	1,000	0*	0*	0*	0*	0*	0*	0*	0*	16	28	0*	0*

19. Hexamethylene-tetramine	5	160	166	22	16	33	28	32	35	11	24	15	28	
	10	157	148	24	16	29	26	28	37	15	25	18	27	
	50	155	171	22	14	18	28	27	38	15	23	16	23	
	100	160	166	22	12	34	30	30	35	8	23	18	25	
	500	165	183	22	14	29	32	29	40	11	21	15	25	
	1,000	142	194	25	12	27	31	44	46	9	13	19	20	
	5,000	231	240	30	12	31	36	54	66	10	21	16	22	
	10,000	296	333	26	16	—	—	87	88	9	11	20	29	
	15,000	—	—	—	—	—	—	104	98	—	—	—	—	
	20. Hexanedioic acid	1	152	179	40	15	58	58	27	33	11	15	15	27
5		148	161	43	17	46	56	30	37	9	20	18	24	
10		151	174	32	19	46	52	26	46	6	18	15	26	
50		155	162	36	19	50	40	23	35	9	15	15	23	
100		179	156	42	23	40	49	29	42	6	16	20	30	
500		154	158	35	14	44	55	31	39	10	18	16	27	
1,000		150	184	37	20	43	50	27	46	7	15	18	23	
5,000		150	177	34	19	42	61	35	31	9	17	15	30	
21. 3-Hydroxy-2-naphthoic acid		1	143	139	36	10	22	23	31	43	10	12	27	32
		5	121	147	30	17	20	25	32	50	11	16	20	31
	10	127	131	40	13	29	26	38	47	11	21	30	31	
	50	108	129	34	16	34	28	28	42	7	15	29	34	
	100	135	134	24	12	22	21	33	54	15	18	31	33	
	500	119	133	39	16	18	22	38	45	11	8	24	41	
	1,000	103	120	31	9	17	27	31	38	7	7	31	35	
	5,000	65*	101	10*	8	7*	8*	6*	10*	0*	0*	7*	22	
	22. Iron(III)chloride	5	147	115	30	23	31	27	27	25	24	29	12	21
		10	138	134	33	25	35	36	28	36	21	36	17	26
50		140	126	31	28	28	33	30	41	19	25	17	21	
100		153	133	35	27	40	28	30	31	28	39	14	23	
500		141	138	23	20	28	24	25	33	22	35	15	16	
1,000		159	129	30	16	30	31	29	36	23	38	13	22	
5,000		125	121	36	24	31	41	25	30	14*	16*	11	13	

23. Isobutyl alcohol	5	154	163	26	19	31	31	21	37	26	32	17	22
	10	156	146	33	25	29	26	26	30	30	24	20	29
	50	165	140	30	16	26	29	18	38	29	33	22	28
	100	160	141	32	16	24	28	22	36	31	36	21	27
	500	163	164	30	19	26	36	22	30	28	37	21	32
	1,000	142	153	27	18	24	31	29	29	25	30	23	20
	5,000	149	130	24	22	33	35	20	23	21	28	32	29
24. Methanol	5	146	162	22	16	31	29	28	38	18	35	14	31
	10	155	164	19	7	36	43	31	37	22	29	17	27
	50	155	180	35	11	28	27	42	33	19	29	13	24
	100	175	161	24	13	30	36	36	37	22	32	16	14
	500	149	177	21	10	32	32	36	32	21	26	18	18
	1,000	159	155	19	16	25	33	27	39	19	29	17	16
	5,000	167	154	20	17	36	31	34	37	22	30	17	20
25. Methyl acetoacetate	1	137	130	36	18	40	39	37	44	17	21	22	23
	5	131	143	35	19	37	44	36	55	16	23	34	29
	10	129	143	28	16	35	35	36	45	14	19	26	27
	50	127	136	29	20	33	38	43	45	14	26	34	24
	100	134	138	37	17	44	39	28	45	17	26	29	35
	500	118	137	31	17	48	41	34	45	18	28	22	30
	1,000	127	153	27	18	37	44	33	45	15	20	28	26
26. 4,4'-Methylene- diphenyl diiso- cyanate	5	153	162	24	11	37	36	31	33	19	11	22	26
	10	142	163	29	13	34	28	25	43	21	16	22	24
	50	148	167	24	11	36	37	32	52	13	24	14	24
	100	136	345	25	21	36	42	30	63	24	21	11	22
	500	160	262	19	11	17	39	34	60	17	19	12	25
	1,000	137*	0*	21	15	26	38	23*	0*	23	27	16	22
	5,000	130*	0*	13*	15	13	31	0*	0*	16	22	16	16

27. 4-Methyl-2-pentanol	1	116	135	39	10	23	38	29	43	13	21	35	28
	5	139	148	38	12	31	25	29	44	14	18	25	30
	10	133	121	35	11	24	29	26	31	17	18	43	25
	50	123	136	41	13	24	31	28	39	22	17	28	34
	100	148	116	39	15	29	25	30	38	12	22	28	38
	500	133	133	38	14	23	35	31	38	15	18	37	35
28. <i>p</i> -Nonylphenol	1,000	136	138	36	12	31	27	21	33	11	11	24	28
	5,000	0*	110*	0*	14*	21*	27*	12*	26*	0*	0*	21*	23*
	0.05	148	170	30	21	45	37	42	45	19	15	13	17
	0.1	135	155	33	18	45	51	34	58	14	27	22	22
	0.5	163	161	38	14	38	47	42	50	15	23	16	17
	1	139	155	35	17	37	45	43	50	15	31	15	28
29. Octadecanoic acid	5	150	182	32	13	42	37	38	47	8	21	11	22
	10	143	185	24*	15	39	35	26	45	7	24	14	21
	50	101*	151	0*	13	27*	42	31*	50	0*	10	0*	30
	100	99*	165	0*	14	20*	45	21*	44	0*	24	0*	23
	1	149	147	27	10	33	31	33	37	14	16	20	25
	5	155	142	21	8	26	35	30	41	20	17	29	28
30. Oleic acid	10	173	127	26	11	21	29	39	24	18	16	27	23
	50	166	149	27	8	32	34	26	37	18	15	26	20
	100	171	152	17	20	24	23	35	34	17	24	18	27
	500	152	172	20	13	23	28	27	33	12	15	17	25
	1,000	150	165	21	14	32	28	29	29	15	15	20	27
	1(0.01) ^a	133	139	24	17	30	36	25	34	14	17	16	23
	5(0.05)	140	141	23	17	25	33	20	40	9	19	16	21
	10(0.1)	141	143	21	13	27	38	22	37	12	19	18	27
	50(0.5)	144	138	23	10	28	35	22	39	11	22	21	28
	100(1)	136	144	17	14	26	33	26	41	10	9	11	23
	500(5)	145	127	16	12	25	32	27	37	6	17	16	26
	1,000(10)	130	115	12	11	20	30	24	47	7*	13	12*	22
	5,000(50)	111	127	17	11	18	26	23	34	7*	11	0*	23
	(100)									4*	10	4*	15

31. Pentaerythritol	5	147	130	30	17	27	30	29	35	19	26	13	19
	10	132	131	33	20	28	31	28	39	15	34	24	29
	50	134	137	31	13	31	28	15	37	15	24	26	19
	100	131	132	27	14	30	34	30	28	17	21	20	27
	500	132	131	31	18	30	30	27	35	19	21	21	26
	1,000	159	130	28	13	31	28	21	33	15	26	18	34
	5,000	145	133	33	14	34	30	23	33	16	24	25	27
32. Pentasodium triphosphate	5	175	170	29	16	22	33	30	54	11	23	21	24
	10	166	172	26	15	25	29	30	63	20	33	26	22
	50	167	158	29	18	24	27	37	53	16	31	27	19
	100	170	165	21	19	30	37	23	48	19	25	25	26
	500	153	182	26	14	30	27	26	49	21	26	27	28
	1,000	158	175	24	14	32	24	30	53	13	17	24	32
	5,000	171	166	21	17	29	23	33	59	12	18	25	21
33. 2-Propanol	5	174	181	26	10	29	32	36	40	14	22	20	29
	10	182	145	25	11	29	30	40	38	17	24	25	29
	50	165	151	26	10	23	36	39	37	14	21	33	34
	100	185	168	24	9	27	25	41	35	10	27	25	28
	500	166	176	21	15	27	29	36	36	12	14	20	34
	1,000	176	158	25	16	33	31	26	35	14	26	17	25
	5,000	173	171	27	10	30	30	38	47	18	22	27	28
34. Sodium dithionite	5	154	144	29	20	21	38	35	36	13	21	15	27
	10	145	136	30	21	33	28	35	31	24	33	22	20
	50	139	127	32	21	35	33	31	25	14	21	15	29
	100	151	129	19	18	25	28	24	29	16	19	16	26
	500	114	134	17	16	24	30	32	32	8	23	13	28
	1,000	114	162	15	12	20	27	38	24	16	28	13	24
	5,000	109	109	16	10	21	27	22	27	8	15	12	14

35. Tetrafluoroboric acid	1	159	160	33	11	32	36	25	33	7	19	22	36	
	5	150	176	36	14	37	33	20	44	7	12	27	37	
	10	130	173	45	9	36	35	22	45	8	12	28	39	
	50	144	147	32	14	36	36	30	40	11	14	30	35	
	100	146	170	46	14	42	36	27	34	5	15	27	40	
	500	143	157	42	12	36	33	29	38	9	14	34	27	
1,000	146	162	38	14	30	39	25	34	13	18	31	36		
	5,000	160	154	36	15	32	28	31	45	10	17	29	33	
36. Tetramethylene-sulfone	1	136	144	38	11	23	30	26	39	11	11	30	32	
	5	142	163	32	18	34	25	21	44	11	12	29	31	
	10	149	170	33	15	25	29	36	38	6	17	33	36	
	50	138	131	32	13	31	26	28	41	10	23	29	37	
	100	133	142	34	17	27	27	28	45	12	15	28	44	
	500	142	149	35	12	27	32	26	36	6	14	30	36	
1,000	141	169	35	13	40	30	28	42	10	13	24	32		
	5,000	131	157	35	12	34	33	25	41	8	9	25	29	
37. Trichloro-isocyanuric acid	0.05	209	174	36	12	30	33	28	38	11	11	31	40	
	0.1	170	192	30	16	30	27	24	34	13	14	35	37	
	0.5	175	174	37	18	24	35	32	32	14	12	30	42	
	1	173	208	37	19	25	33	27	40	10	12	32	40	
	5	159	182	31	15	33	38	37	42	10	12	38	32	
	10	168	159	37	17	40	30	27	41	13	12	28	33	
50	139	189	20	16	36	29	18*	32	32	8	18	20*	29	
	100	101*	174	5*	19	26*	38	13*	52	0*	8	0*	42	
	500	0*	278	0*	23*	0*	32*	0*	41	0*	0*	0*	43	
	38. Urea	5	143	178	28	18	27	35	41	44	14	15	23	30
		10	167	162	24	17	25	29	36	34	14	13	24	28
		50	143	171	22	19	33	38	26	32	16	17	26	25
100		164	157	23	17	31	35	30	43	9	15	34	27	
500		158	187	30	20	37	34	36	40	10	13	25	33	
1,000		161	154	35	11	33	26	35	42	16	21	22	28	
5,000	134	175	27	18	25	32	35	41	12	18	31	30		

39. <i>p</i> -Xylene	1	139	161	28	9	21	31	38	35	9	22	36	30
	5	156	173	23	8	25	24	39	41	12	27	23	25
	10	134	151	20	11	25	35	28	36	8	21	26	30
	50	134	151	14	7	26	26	26	34	10	24	30	27
	100	138	151	0*	7	23	25	35	36	11	25	24	30
	500	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*
	1,000	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*	0*

ex. 149 ± 17.1^a; Mean ± S.D. —^b: not tested. *e: growth inhibition was observed. ()^a: concentrations in parenthesis were used in TA1537 and TA1538.

The dominant lethal mutation in C3H male mice given the substance orally at a dose of 25,000 mg/kg body weight was reported to be positive but negative at 800–1,500 mg/kg body weight when administered intraperitoneally.⁶⁾ Mammary and pituitary tumors were induced in rats given drinking water containing 0.1% HMT,⁷⁾ and multiple malignant tumors were observed in rats given HMT subcutaneously,⁸⁾ but not in mice.⁹⁾ On the other hand, there are negative reports on rats and mice given drinking water containing HMT.¹⁰⁾ No malformation was observed in rats given drinking water containing 1% HMT for two weeks before mating or during pregnancy and lactation.¹¹⁾ The output of this chemical in Japan was 21 million kilograms in 1979 and 13 million kilograms in 1982.¹²⁾

MDI was mutagenic to *S. typhimurium* TA100 and slightly mutagenic to TA98 by metabolic activation. These results were in agreement with those reported previously.^{13,14)} This compound gave positive results at 100 µg/plate. Inhibition of bacterial growth was observed in 1,000 µg/plate in both *Salmonella* and *E. coli*. On the other hand, negative results were reported by the National Toxicology Program.¹⁵⁾ Carcinogenicity and teratogenicity of MDI have not been reported so far in animals or human subjects.¹⁴⁾ The production of this chemical in Japan was 44 million kilograms in 1979 and 70 million kilograms in 1983.¹²⁾

The carcinogenicity of isobutyl alcohol (IBA) was confirmed in 1975 by Gibel *et al.*,¹⁶⁾ but this compound did not demonstrate any mutagenicity. Eight malignant and three benign tumors were produced in 24 Wistar rats by subcutaneous administration of IBA, and three malignant and nine benign tumors were induced in 19 Wistar rats by oral administration. On the other hand, there is a negative report of tumor induction in four rats given IBA orally.¹⁷⁾

No tumor was produced in mice given 2-propanol (PRO) by subcutaneous injection, inhalation, skin painting¹⁸⁾ or oral administration.¹⁷⁾ An epidemiological report was published on the incidence of cancer of the paranasal sinuses and the larynx in workers in factories manufacturing PRO by strong acid process.¹⁹⁾

Urea is used widely in the chemical industry as a material for nitrogen fertilizers, medicines, celluloid stabilizers, paint, etc., and its output in Japan was

1.2 million kilograms in 1981.¹²⁾ Chromosomal aberration of mammalian cells caused by urea was observed in *in vitro* tests,²⁰⁾ but no DNA damage was noted in alkaline elution/rat hepatocyte assays.²¹⁾ No mutagenic activity was observed in our mutagenicity test. In spite of the induction of chromosome aberration, no carcinogenicity was observed in rats and mice.²²⁾

Methanol did not demonstrate mutagenicity in cell transformation,²³⁾ sister chromatid exchange²⁴⁾ or *Saccharomyces cerevisiae* tests,²⁵⁾ and no carcinogenicity was found in mice,²⁶⁾ rats or dogs. *p*-Xylene is not mutagenic.²⁷⁻²⁹⁾ 2-Butane,^{9,30)} glycerol,^{8,11,28,29)} 2-ethoxyethanol^{9,31)} and oleic acid^{9,11,15,17,32,33)} were tested for mutagenicity and carcinogenicity with negative results.

Hexanedioic acid showed weak mutagenicity in the host-mediated assay using *Saccharomyces* D₃, but did not present any mutagenicity in *in vitro* tests using *Saccharomyces* D₃, TA1530 and G46 strains.³⁴⁾ The results of cytogenetic chromosomal aberration test³⁴⁾ and dominant lethal test³⁴⁾ in rats were negative.

2-Methylpropane, a gaseous compound, was not mutagenic to *Salmonella*, *E. coli*, mouse lymphoma cells or mouse embryo fibroblasts.³⁵⁾ Carcinogenicity of this compound has not yet been reported.

The carcinogenicity of dodecyl benzene,³⁶⁾ dodecanol,³⁷⁾ iron chloride,^{9,38)} ammonia⁹⁾ and octadecanoic acid^{9,11,17,38)} was tested with negative results.

CONCLUSION

More than 500 new chemical compounds have been registered at the Ministry of Labor in Japan Since 1979, and obligatory microbial mutation tests have been performed on these chemicals. Testing of the mutagenicity and carcinogenicity of chemicals selected from 45,000 chemicals with consideration given to their structure and annual output have recently been started. The 43 compounds tested by us were registered before 1979 and are manufactured in annual quantities of more than one million kilograms by the chemical industry. Considering the importance of testing the mutagenic activities of these 43 chemicals, using six strains of bacteria according to the Ministry of Labor guidelines because of their high production, our investigation was carried out, and it was

found that only two of the 43 compounds were mutagenic.

This work was supported by Japan Chemical Industry Ecology-Toxicology & Information Center.

REFERENCES

- 1) Ames, B.N., McCann, J. and Yamasaki, E.: Methods for detecting carcinogens and mutagens with the salmonella/mammalian microsome mutagenicity test. *Mutat. Res.*, 31: 347-364, 1975.
- 2) Yahagi, T., Nagao, M., Seino, Y., Matsushima, T., Sugimura, T. and Okada, M.: Mutagenicity of N-nitrosoamine of Salmonella, *Mutat. Res.*, 48: 121-130, 1977.
- 3) McCann, J. and Ames, B.N.: Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals: discussion, *Proc. Natl. Acad. Sci. USA*, 73: 950-954, 1976.
- 4) Sugimura, T., Sato, S., Nagao, M., Yahagi, T., Matsushima, T., Seino, Y., Takeuchi, M. and Kawachi, T.: Overlapping of carcinogens and mutagens. In P.N. Magee (ed.), *Fundamentals in Cancer Prevention*, 191-215, University of Tokyo Press, Tokyo/Univ. Park Press, Baltimore, 1976.
- 5) Matsushita, H., Goto, S. and Hamano, Y.: Mutagenicity testing method for volatile compounds, *Japan, J. Ind. Health*, 23: 761, 1981.
- 6) U.S. Department of Commerce, National Technical Information Service, PB-274 264: A study of industrial data on candidate chemicals for testing, 3-135-138, Environmental Protection Agency, Washington, D.C., 1977.
- 7) Lijinsky, W. and Taylor, H.W.: Nitrosamines and their precursors in food. In (H.H. Hiatt, J.D. Watson and J.A. Winsten, eds.), *Origin of Human Cancer*; 1579-1590, Cold Spring Harbor Laboratory, University of Tokyo Press, Tokyo, 1977.
- 8) Watanabe, F. and Sugimoto, S.: Study on the carcinogenicity of aldehyde. 2nd report. Seven cases of transplantable sarcomas of rats appearing in the areas of repeated subcutaneous injection of Urotropin, *Gann*, 46: 365-367, 1955.
- 9) Survey of Compounds Which Have Been Tested for Carcinogenic Activity, 2nd edition, Federal Security Agency, Public Health Service, 1951.
- 10) Della Porta, G., Colnaghi, M.I. and Parmiani, G.: Non-carcinogenicity of hexamethylenetetramine in mice and rats, *Fd. Cosmet. Toxicol.*, 6: 707-715, 1968.
- 11) Survey of compounds which have been tested for carcinogenic activity, 1970-1971, U.S. Department of Health, Education and Welfare, Public Health Service, National Cancer Institute of Health.

Table 5. Mutagenic activities

No.	Compound	Dose	Revertant			
			TA100		TA1535	
			—S9	+S9	—S9	+S9
	Control	0	191.8±39.5 ^a	190.6±49.3	31.3±7.0	27.8±8.4
	2NF	2 µg/plate	700±52.8	— ^b	—	—
	ENNG	5 "	—	—	1001.4±168.5	—
	9AC	80 "	—	—	—	—
	B(a)P	5 "	—	—	—	—
		2.5 "	—	956.4±212.4	—	—
	2AA	4 "	—	—	—	—
		2 "	—	—	—	138.5±24.8
1.	Ammonia	500 ppm	243	229	25	31
		1,000 "	251	220	23	40
		2,500 "	198	181	29	35
		5,000 "	207	195	20	21
		10,000 "	197	185	23	34
		25,000 "	227	220	19	31
2.	Butane	250 ppm	216	233	25	28
		625 "	153	236	24	27
		1,250 "	237	234	25	30
		2,500 "	243	206	20	23
		5,000 "	205	233	26	25
		10,000 "	219	254	28	39
3.	Chlorine	0.5 ppm	93	119	42	43
		1.0 "	92	130	45	43
		2.5 "	92	115	38	37
		5.0 "	111	132	40	35
		10.0 "	120	133	34	41
		25.0 "	82 ^{*c}	133	34 [*]	41
4.	2-Methylpropene	250 ppm	180	219	48	27
		625 "	197	214	53	38
		1,250 "	178	225	52	44
		2,500 "	243	251	43	33
		5,000 "	260	252	37	31
		10,000 "	228	267	28	31

ex. 191.8±39.5^a: Mean±S.D. —^b: not tested. ^{*c}: growth inhibition was observed.

of 4 volatile compounds.

colonies/plate							
WP2 uvrA		TA98		TA1537		TA1538	
—S9	+S9	—S9	+S9	—S9	+S9	—S9	+S9
32±5.0	28.8±6.1	48.3±7.7	60.7±14.1	11.4±3.0	10.3±3.8	31.8±8.6	58.3±14.2
—	—	503.3±121.9	—	—	—	295.6±46.5	—
136.8±39.8	—	—	—	—	—	—	—
—	—	—	—	745±59.1	—	—	—
—	—	—	546±29.8	—	96.8±24.6	—	510.5±183.8
—	—	—	389.5±43.3	—	—	—	—
—	132±50.7	—	—	—	—	—	—
—	—	—	—	—	—	—	—
36	31	64	63	11	9	13	37
32	33	56	76	13	7	27	59
28	31	43	66	8	9	23	53
33	28	43	53	10	6	34	55
33	30	69	60	7	13	32	52
19	20	57	68	13	10	25	40
41	42	47	59	10	9	34	52
41	43	53	65	10	9	30	65
51	51	64	74	17	29	41	63
46	61	46	77	22	31	26	58
33	39	46	56	19	19	34	58
22	29	52	81	10	14	22	55
27	26	28	48	12	9	39	65
29	30	37	55	12	10	33	57
21	27	38	44	11	10	28	62
15	27	37	53	11	8	42	67
11	25	45	52	5	2	32	53
25	24	13*	59*	2*	3	27*	52*
43	40	47	67	12	11	35	55
44	46	47	77	11	10	34	53
46	51	67	75	16	21	33	35
52	62	55	87	18	30	20	52
32	42	68	84	25	17*	23	56
28	35	37	92	12*	20*	23	66

- 12) Year Book of Chemical Industry's Statistics: 1979-1984. The Ministry of International Trade and Industry, Tokyo.
- 13) Andersen, M., Binderup, M.L., Kiel, P., Larsen, H. and Maxild, J.: Mutagenic action of isocyanates used in the production of polyurethanes, *Scand. J. Work Environ. Health*, 6: 221-226, 1980.
- 14) Woolrich, P.F.: Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPi, *Am. Ind. Hyg. Assoc. J.*, 43: 89-97, 1982.
- 15) National Toxicology Program of Department of Health and Human Services: NTP Technical Bulletin, No. 6, 1982.
- 16) Gibel, W., Lohs, Kh. and Wildner, G.P.: Experimentelle Untersuchungen zur kanzerogenen Wirkung von Lösungsmitteln am Beispiel von Propanol-1, 2-methylpropanol-1 und 3-methylbutanol-1, *Arch. Geschwulstforsch.*, 45: 19-24, 1975.
- 17) Survey of compounds which have been tested for carcinogenic activity. Supplement 2, U.S. Department of Health, Education and Welfare, PHS, NCI, NIH, 1969.
- 18) Weil, C.S., Smyth, H.F., Jr. and Nale, T.W.: Quest for suspected industrial carcinogen, *AMA Arch. Ind. Hyg.*, 5: 535-547, 1952.
- 19) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, IARC Monogr. Suppl., 4: 151 (IARC, Lyon, France) 1982.
- 20) Ishidate, M., Sofuni, T. and Yoshikawa, K.: Chromosomal aberration tests *in vitro* as a primary screening tool for environmental mutagens and/or carcinogens, *Gann Monogr.*, 27: 95-108, 1981.
- 21) Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. and Bradley, M.O.: Evaluation of the alkaline elution/rat hepatocytes assay as a prediction of carcinogenic/mutagenic potential, *Mutat. Res.*, 113: 357-391, 1983.
- 22) Fleischman, R.W., Baker, J.R., Hagopian, M., Wade, G.C., Hayden, D.W., Smith, E.R., Weisburger, J.H. and Weisburger, E.K.: Carcinogenesis bioassay of acetamide, hexanamide, adipamide, urea and *p*-tolylurea in mice and rats, *J. Environ. Pathol. Toxicol.*, 3: 149-170, 1980.
- 23) Pienta, R.J., Poiley, J.A. and Lebhera, B., III.: Morphological transformation of early passage golden Syrian hamster embryo cells derived from cryopreserved primary cultures as a reliable *in vitro* bioassay for identifying diverse carcinogens, *Int. J. Cancer*, 19: 642-655, 1977.
- 24) Latt, S.A., Allen, J., Bloom, S.E., Carrano, A., Fiske, E., Kram, D., Schneider, E., Schreck, R., Tice, R., Whitfield, B. and Wolff, S.: Sister-chromatid exchange: a report of the Gene Tox Program, *Mutat. Res.*, 87: 17-62, 1981.
- 25) Abbondandolo, A., Bonatti, S., Corsi, C., Corti, G., Florio, R., Leporini, C., Mazzaccaro, A. and Nieri, R.: The use of organic solvents in mutagenicity testing, *Mutat. Res.*, 79: 141-150, 1980.
- 26) Survey of compounds which have been tested for carcinogenic activity, 1974-1975 volume, U.S. Department of Health, and Human Services, PHS, NIH.
- 27) Bos, R.P., Drouns, R.M.G., von Doorn, R., Theuws, T.L.G. and Henderson, P.T.H.: Non mutagenicity of toluene, *o*, *m*, and *p*-xylene, *o*-methylbenzylalcohol and *o*-methylbenzylsulfate in the Ames assay, *Mutat. Res.*, 88: 273-279, 1981.
- 28) National Toxicology Program of Department of Health and Human Services: NTP Technical Bulletin, Vol. 1, 1980.
- 29) Haworth, S., Lawler, T., Mortelmans, K., Speck, W. and Zeiger, E.: Salmonella mutagenicity test results for 250 chemicals, *Environ. Mutagen., Supplement* 1: 3-142, 1983.
- 30) Nestmann, E.R., Lee, E.G.H., Matula, T.I., Douglas, G.R. and Mueller, J.C.: Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian microsome assay, *Mutat. Res.*, 79: 203-212, 1980.
- 31) National Toxicology Program of Department of Health and Human Services: NTP Technical Bulletin No. 5, 1981.
- 32) Survey of compounds which have been tested for carcinogenic activity, 1961-1967 volume, U.S. Department of Health, Education and Welfare, PHS, NIH.
- 33) Survey of compounds which have been tested for carcinogenic activity, 1972-1973 volume, U.S. Department of Health and Human Services, PHS, NIH, Bethesda, Md.
- 34) Mutagenic evaluation of compound FDA 71-50, Adipic acid, Food and Drug Administration, PB-245 466, 1974, U.S. Department of Commerce, National Technical Information Service.
- 35) Staab, R.J., and Sarginson, N.J.: Lack of genetic toxicity of isobutylene gas, *Mutat. Res.*, 130: 259-260, 1984.
- 36) Gargus, J.L., Paynter, O.E. and Reese, W.H., Jr.: Utilization of newborn mice in the bioassay of chemical carcinogens, *Toxicol. Appl. Pharmacol.*, 15: 552-559, 1969.
- 37) Sice, J.: Tumor-promoting activity of *n*-alkanes and 1-alkanols, *Toxicol. Appl. Pharmacol.*, 9: 70-74, 1966.
- 38) Nagata, C., Tagashira, Y., Kodama, M., Ioki, Y. and Oboshi, S.: Effect of hydrogen peroxide, Fenton's reagent and iron ions on the carcinogenicity of 3,4-benzopyrene, *Gann*, 64: 277-285, 1973.

和 文 要 旨

わが国で生産使用される化学物質のうち、年間 1,000 トン以上の生産量を示す43物質を選び、*S. typhimurium*

TA100, TA98, TA1535, TA1537, TA1538 および *E. coli* WP2 *uvrA* の6菌株を用いて突然変異原性試験を行った。

テストした43物質のうち39物質は、粉末または非揮発性液体で、このうち2物質のみが陽性を示した。その一つの hexamethylenetetramine は、TA100 および TA98 に対して S9mix 存在下で、また TA98 では S9mix 非存在下で陽性を示した。もう一つの 4,4'-methylene-diphenyldiisocyanate は、TA100 と TA98 の2菌株で S9mix 存在下で陽性を示した。

一方これら43物質のうち、ガス状または揮発性の高い4物質は、ガス暴露法を用いて試験を行ったが、いずれの結果も陰性であった。試験をした43物質のうち41物質が6菌株に対して陰性であったが、文献上なんらかの変異原性試験結果が報告されているものは11物質(25.6%)にすぎない。今回選択した43物質間には化学構造上の類似性はないが、年間生産量が高く、職業性暴露の可能性も高いので、変異原性試験を行い、その結果を報告することは有意義であると考える。

Reprint requests to Department of Public Health, The Jikei University School of Medicine,
Minato-ku, Tokyo, 105 Japan (H. Shimizu) 著者への通信先: 清水英佑 〒105 東京都港区西新
橋3-25-8 東京慈恵会医科大学公衆衛生学教室