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U.S. Environmental Protection Agency
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BEHQ-01-14908

Dear 8(e) Coordinator:

This letter is to inform you of a publication that recently came to our attention concerning inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice (methyl bromide, carbon tetrachloride, chloroform, tetrachloroethylene, 1,2-dichloroethane and p-dichlorobenzene) conducted by the Japan Bioassay Research Center.

Enclosed please find a copy of the published article and an abstract of these studies.

Sincerely,

A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

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Proceedings of the 1st ASIATOX Conference, June 29-July 2, 1997, Yokohama, Japan

P-005

LONG TERM INHALATION TOXICITY STUDIES
OF FIVE CHLORINATED HYDROCARBONS IN
F344 RATS AND BDF1 MICE

Taijiro MATSUSHIMA, Kasuke NAGANO,
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Long term inhalation toxicity studies of five chlorinated hydrocarbons were conducted by exposure groups (three dose groups) of 50 male and 50 female F344 rats and BDF1 mice, 6 hours per day, 5 days per week for 104 weeks to air containing each chemicals.

Carbon tetrachloride induced hepatocellular carcinomas/adenomas in rats and mice and also induced pheochromocytomas in mice adrenal glands. Chloroform induced renal-cell carcinomas/adenomas in male mice and hepatocellular carcinomas in female mice. Tetrachloroethylene induced mononuclear cell leukemias in both sex of rats, hepatocellular carcinomas/adenomas in both sex of mice and Harderian gland adenomas in male mice.

1,2-Dichloroethane induced fibroadenomas of the mammary gland and fibromas of the subcutis in both sex of rats, adenocarcinomas/adenomas in female rats mammary gland, mesotheliomas in male rats peritoneum, hemangiosarcomas in male mice liver, and hepatocellular adenomas, bronchiolar-alveolar carcinomas/adenomas of the lung, adenocarcinomas of the mammary gland and endometrial stromal polyps of the uterus in female mice. p-Dichlorobenzene induced hepatocellular carcinomas and histiocytic sarcomas in male mice, and hepatocellular carcinomas/adenomas and bronchiolar-alveolar carcinomas in female mice.

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Advances in the Prevention of Occupational Respiratory Diseases

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Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice

Kasuke Nagano, Tomoshi Nishizawa, Seigo Yamamoto and Taijiro Matsushima

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Abstract. Inhalation carcinogenesis studies of six halogenated hydrocarbons were conducted by exposure to air containing each chemical of three dose groups of 50 male and 50 female F344 rats and BDF1 mice, 6 h per day, 5 days per week for 104 weeks. Methyl bromide did not induce neoplasms, but produced damages in the nasal cavity of rats and mice. Carbon tetrachloride induced hepatocellular carcinomas/adenomas in rats and mice and also induced pheochromocytomas in mice adrenal glands. Chloroform induced renal cell carcinomas/adenomas in male mice and hepatocellular carcinomas in female mice. Tetrachloroethylene induced mononuclear cell leukemias in both sexes of rats, hepatocellular carcinomas/adenomas in both sexes of mice and Harderian gland adenomas in male mice. 1,2-dichloroethane induced fibroadenomas of the mammary gland and fibromas of the subcutis in both sexes of rats, adenocarcinomas/adenomas in the mammary gland of female rats, mesotheliomas in the peritoneum of male rats, hemangiosarcomas in male mice liver, and hepatocellular adenomas, bronchiolar-alveolar carcinomas/adenomas of the lung, adenocarcinomas of the mammary gland and endometrial stromal polyps of the uterus in female mice. Hepatocellular carcinomas and histiocytic sarcomas were induced by *p*-dichlorobenzene in male mice, and it induced hepatocellular carcinomas/adenomas and bronchiolar-alveolar carcinomas in female mice.

Keywords: 1,2-dichloroethane, carbon tetrachloride, chloroform, methyl bromide, *p*-dichlorobenzene, tetrachloroethylene.

Introduction

The Japan Bioassay Research Center was established by the Ministry of Labour in 1982 with the object of supporting private companies in researching the toxicity of new chemicals prior to their industrial application and with the aim of examining the adverse effects of existing chemical substances under an effort of the Ministry of Labour. The Japan Bioassay Research Center is the only facility in Japan to perform carcinogenicity studies by means of inhalation. This method is required as harmful substances in the work place are generally inhaled into the body through respiration. Thirty chemicals in the past 15 years have been tested or are currently being tested for carcinogenicity by inhalation or by oral administration in both rats and mice. In this presentation, we introduce the result

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of the inhalation carcinogenesis studies of six halogenated hydrocarbons conducted at the Japan Bioassay Research Center under contract with the Ministry of Labour.

Materials and Methods

Chemicals and animals

Methyl bromide (purity >99.9%) was obtained from Sanko Chemical Co., contained in compressed-gas cylinders. Another five chemicals were obtained as special grade (Japan Industrial Standard, 99% (gc)) from Wako Pure Chemical Industries, Ltd. (Purity: carbon tetrachloride, chloroform, tetrachloroethylene and 1,2-dichloroethane >99%, p-dichlorobenzene >99.9%) as a liquid in 500-g bottles.) Male and female F344 rats (SPF) and BDF1 mice (SPF) were obtained from Charles River Japan Inc., at 4 weeks of age. After 2 weeks acclimatization, the animals were randomly allocated to each group.

Exposure chambers and animal maintenance

Chambers for rats (vol.: 7,600 l) and mice (vol.: 3,700 l) were used throughout the duration of the exposure period. The temperature ($24 \pm 2^\circ\text{C}$), the relative humidity ($55 \pm 10\%$), air flow rate (rat: 1,900 l/min, mouse: 740 l/min) and pressure ($-5 \sim -15 \text{ mm H}_2\text{O}$) of the chamber were monitored each day at 1-h intervals for each group. Animals were housed individually in wire mesh cages. Feed (CRF-1, Oriental Yeast Co., Ltd.) and water were available ad libitum.

Generation and monitoring of chamber concentration

Methyl bromide gas was generated from the cylinder and was made by dilution with fresh air in the line mixer to the target concentration of each exposure chamber. The vapor of the other five chemicals was generated from the reservoir by heating with the constant temperature circulator and at the same time bubbling with fresh air. The vapor was stabilized by cooling to the dew point and again heating, and was made by dilution with fresh air in the line mixer to the target concentration of each exposure chamber. The concentration of chemicals in each chamber was monitored at least every 15 min by gas chromatography.

Experimental design

A maximum tolerated dose was selected as the highest dose level for each study based on the 2-week and 13-week preliminary studies. The target concentrations of each chemical were shown in Table 1. Groups of 50 male and 50 female rats and mice were exposed to air containing chemicals 6 h per day, 5 days per week for 104 weeks. Groups of 50 rats and 50 mice of each sex, serving as controls,

Table 1. Summary of neoplastic lesions in 2-year inhalation studies of six halogenated hydrocarbons in F344 rats and B6D mice.

Test substances	Species/ sexes	Dose (ppm)	Results ^a				
			0	4	20	100	
Methyl bromide	Rats	Pituitary gland adenoma	16/50	23/50	19/50	30/50	
			No increase in tumor incidence				
	Mice		No increase in tumor incidence				
			No increase in tumor incidence				
	Carbon tetrachloride	Rats	Hepatocellular adenoma	0/50	1/50	1/50	21/50
			Hepatocellular carcinoma	1/50	0/50	0/50	32/50
Mice		Hepatocellular adenoma	0/50	0/50	0/50	40/50	
		Hepatocellular carcinoma	0/50	0/50	3/50	15/50	
Chloroform		Rats	Hepatocellular adenoma	9/50	10/50	27/50	16/50
			Hepatocellular carcinoma	17/50	12/50	44/50	47/50
		Mice	Adrenal gland pheochromocytoma	0/50	0/50	16/50	31/50
			Hepatocellular adenoma	2/50	8/49	17/50	5/49
		Mice	Hepatocellular carcinoma	2/50	1/49	33/50	48/49
			Adrenal gland pheochromocytoma	0/50	0/49	0/50	22/49
Tetrachloroethylene	Rats		No increase in tumor incidence				
			No increase in tumor incidence				
	Mice		No increase in tumor incidence				
			No increase in tumor incidence				
	Rats	Renal cell adenoma	0/50	0/50	3/50	1/48	
		Renal cell carcinoma	0/50	1/50	4/50	11/48	
	Mice	Hepatocellular carcinoma	1/50	1/50	0/50	3/50	
			No increase in tumor incidence				
	Tetrachloroethylene	Rats	Dose (ppm)	0	50	200	600
			Mononuclear cell leukemia	11/50	14/50	22/50	27/50
Mice		Mononuclear cell leukemia	10/50	17/50	16/50	19/50	
			No increase in tumor incidence				
Mice		Hepatocellular adenoma	7/50	13/50	8/50	26/50	
		Hepatocellular carcinoma	7/50	8/50	12/50	25/50	
Mice	Harderian gland adenoma	2/50	2/50	2/50	8/50		
	Hepatocellular adenoma	3/50	3/47	7/49	26/49		
Mice	Hepatocellular carcinoma	0/50	0/470	0/49	14/49		

(continued.)

were exposed to clean air in chambers. Animals were observed daily for clinical signs and for mortality once a day. Animals were weighed weekly for the first 13 weeks of the study and every 4 weeks thereafter. At week 105, all surviving animals were killed, and a complete necropsy was performed on each animal. A thorough necropsy was also performed on animals that were found dead or

Table I. Continued.

Test substances	Species/ sexes	Dose (ppm)	Results ^a			
1,2-Dichloroethane	Rats Male	Dose (ppm)	0	10	40	160
		Mammary gland fibroadenoma	0/50	0/50	1/50	5/50
	Female	Subcutaneous tissue fibroma	6/50	9/50	12/50	15/50
		Peritoneum mesothelioma	1/50	1/50	1/50	5/50
		Mammary gland adenoma	3/50	5/50	5/50	11/50
		Mammary gland fibroadenoma	4/50	1/50	6/50	13/50
		Mammary gland adenocarcinoma	1/50	2/50	0/50	5/50
		Subcutaneous tissue fibroma	0/50	0/50	1/50	5/50
	Mice	Dose (ppm)	0	10	30	90
	Male	Liver hemangiosarcoma	0/50	4/49	6/50	5/50
		Female	Hepatocellular adenoma	1/49	1/50	1/50
	Bronchiolar-alveolar adenoma		4/49	1/50	3/50	8/50
	Bronchiolar-alveolar carcinoma		1/49	0/50	1/50	3/50
	Mammary gland adenocarcinoma		1/49	2/50	1/50	6/50
Uterus endometrial stromal polyp	2/49		0/50	1/50	6/50	
			0	20	75	300
p-Dichlorobenzene	Rats	Dose (ppm)	0	20	75	300
	Male		No increase in tumor incidence			
		Female		No increase in tumor incidences		
	Mice		Dose (ppm)	0	20	75
		Male	Hepatocellular carcinoma	12/49	17/49	16/50
	(with hepatoblastoma-like feature)		(0/12)	(2/17)	(1/16)	(8/38)
	Female	Liver histiocytic sarcoma	0/49	3/49	1/50	6/49
		Hepatocellular adenoma	2/50	10/50	6/49	20/50
		Hepatocellular carcinoma	2/50	4/50	2/49	4/50
(with hepatoblastoma-like feature)		(0/2)	(0/4)	(0/2)	(6/41)	
	Bronchiolar-alveolar carcinoma	1/50	1/50	1/49	4/50	

were killed in moribund condition during the study. All organs and gross lesions were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin for histopathological examination.

Statistical method

Neoplastic lesions at histopathology were analyzed by Peto test [1], Cochran-Armitage linear trend test, and the Fisher exact test.

Results

Methyl bromide

Rat

Although increased incidence of adenoma in the pituitary glands was observed in

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