

Effects of long-term oral administration of styrene to mice and rats

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PONOMARKOV, V. and TOMATIS, L. Effects of long-term oral administration of styrene to mice and rats. *Scand. j. work environ. & health* 4 (1978): suppl. 2, 127—135. Styrene monomer dissolved in olive oil was given orally to female O₂₀ mice (1,350 mg/kg), C₅₇ Bl mice (300 mg/kg) and BD IV rats (1,350 mg/kg) on the 17th day of gestation. Their offspring were treated weekly with styrene by stomach tube from the time of weaning throughout their life-span. The weekly doses used were 1,350 mg/kg for O₂₀ mice, 300 mg/kg for C₅₇ Bl mice, and 500 mg/kg for BD IV rats. Following the continuous oral administration of styrene for over 100 weeks, an increased and earlier appearance of lung tumors was observed in O₂₀ mice. A few tumors rarely seen in controls were observed in BD IV styrene-treated rats, and a slightly increased incidence of liver tumors was found in C₅₇ Bl mice. In both cases, however, the total incidence of tumors was not significantly different from that of the controls. The present results provide weak evidence of the carcinogenicity of styrene in one of the two strains of mice tested, when it is given at a high dose level.

Key words: acute toxicity, carcinogenicity, mice, rats, styrene.

Styrene monomer is a chemical widely used for the production of plastics and resins. Its world production in 1976 was about 7 million tons.

Acute toxic effects in man following occupational exposure to styrene have been reported, for example, slight leucopenia with lymphocytosis, irritation of the skin, the eyes and the respiratory tract, and depression of the central nervous system (1, 5, 7). The only available report on long-term effects of styrene in humans indicates a possible increased frequency of leukemia and lymphomas in workers involved in the production of styrene (2).

The acute toxicity of styrene in rodents is low, the acute oral LD₅₀² in rats being 5 g/kg of body weight (7) and the respective intraperitoneal LD₅₀ being 2.5 g/kg of body weight (4). Long-term tests with rats were carried out by inhalation and feeding (7). However, the observation period in this study was limited to no more than six months, and therefore the results are inadequate for the evaluation of the possible carcinogenicity of styrene. In the present report, the results of long-term carcinogenicity testing of styrene in mice and rats are given.

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² LD₅₀ = mean lethal dose.

MATERIAL AND METHODS

Inbred O₂₀ and C₅₇ Bl mice, originally obtained from The Netherlands Cancer Institute, and inbred BD IV rats, originally provided by Prof. H. Druckrey (Freiburg, Federal Republic of Germany), were used in the experiments. The animals were kept in Makrolon cages N111 under normal laboratory conditions and were maintained on Charles River food pellets. Water was available *ad libitum*. Samples of the food were analyzed twice during the course of the experiment by the Tropical Products Institute, London, which assessed the possible presence of aflatoxins; none were detected. Samples were also analyzed twice for the presence of nitrosamines (the analysis was carried out by Dr. Preussmann of the Deutsches Krebsforschungszentrum). Nitrosamines were present at levels of 0.2–0.6 parts per billion.

Styrene monomer, provided by Riedel de Haënag Seelze (Federal Republic of Germany) (99 % pure), was dissolved in olive oil and administered to the animals by stomach tube. The same schedule of treatment was chosen for both the mouse and rat experiments, i.e., single oral administration of styrene to females on the 17th day of gestation and continuous weekly oral treatment to their offspring from the time of weaning for their lifespan.

Twenty-nine O₂₀ female mice were given a styrene dose of 1,350 mg/kg of body weight dissolved in 0.1 ml of olive oil by stomach tube once on the 17th day of pregnancy. After weaning, their progeny received the same dose once a week. The treatment had to be suspended after 16 weeks because of toxicity. Nine O₂₀ females, serving as controls, were given a single administration of 0.1 ml of olive oil on the 17th day of pregnancy and their progeny received a weekly administration of 0.1 ml of olive oil for life, beginning after weaning. A separate group of 54 males and 47 females received no treatment and served as untreated controls.

Fifteen C₅₇ Bl female mice were given a styrene dose of 300 mg/kg of body weight dissolved in 0.1 ml of olive oil by stomach tube once on the 17th day of pregnancy, and their progeny received the

same dose once a week for life, beginning after weaning. Twelve males and 13 females, the progeny of five C₅₇ Bl mice given a single oral administration of 0.1 ml of olive oil on 17th day of pregnancy, received weekly doses of 0.1 ml of olive oil for life beginning after weaning. A group of 51 male and 49 female C₅₇ Bl mice served as untreated controls.

Twenty-one female BD IV rats were given a single dose of 1,350 mg/kg of body weight of styrene in olive oil by stomach tube on the 17th day of pregnancy, and their progeny received weekly styrene doses of 500 mg/kg of body weight in 0.3 ml of olive oil. Ten female BD IV rats received 0.3 ml of olive oil on the 17th day of pregnancy, and their progeny received weekly doses of 0.3 ml of olive oil for life beginning after weaning.

All survivors were killed at 120 weeks, and until then animals were killed only when moribund. All animals were autopsied and all major internal organs, as well as those showing gross abnormalities, were examined histologically. Sections were stained with hematoxylin-eosin routinely and special stains were used whenever necessary.

RESULTS

In order to establish the LD₅₀ for animals used in the present experiment, we gave groups of four O₂₀ and C₅₇ Bl mice and BD IV rats single oral doses of 50–7,200 mg/kg of styrene in olive oil. None of the animals treated died within 15 d of treatment.

O₂₀ mice

The litter size was similar in all the groups of the O₂₀ mice, but the preweaning mortality was considerably higher in the styrene-treated group than in the olive oil-treated group (43 % versus 22 %).

The survival rates are summarized in table 1. Mortality was high among the

Table 1. Survival rates O₂₀ mice treated with styrene and controls.

Group	Initial number	Number of survivors (weeks)											
		10	20	30	40	50	60	70	80	90	100	110	120
Females given styrene	29	29	29	24	22	22	21	18	14	10	7	2	
Progeny treated weekly with styrene													
Male	45	38	22	21	18	13	5	2	1				
Female	39	34	32	32	29	19	10	6	6	2	1		
Females given olive oil	9	9	9	9	9	9	9	7	7	3	2	1	
Progeny treated weekly with olive oil													
Male	20	19	19	19	19	19	17	17	15	11	10	2	
Female	22	22	22	22	22	22	18	14	13	10	9	3	
Untreated controls													
Male	54	54	54	54	53	52	52	48	46	34	21	12	7
Female	47	47	47	47	47	47	46	44	40	32	26	12	6

Table 2. Tumor incidence in O₂₀ female mice treated with styrene on the 17th day of pregnancy, their progeny receiving weekly treatments for life, and controls.

Group	Initial number	Average age at death ^a (weeks)	Effective number ^b	TBA ^c		Number of tumors		More than one tumor		Lung tumor			First lung tumor appeared (weeks)	Average age of animals with lung tumor	Other tumors	
				N	% ^d	N	Per mouse ^d	N	% ^d	Ade-noma	Carci-noma	Total number			N	% ^d
												% ^d				
Females given styrene	29	73.7	20	13	65.0	14	0.7	1	5	4	7	11	55	65	85.8	2 ^e 10
Progeny treated with styrene																
Male	45	32.4	23	20	89	22	0.9	2	8.7	12	8	20	89	21	48.8	2 ^f 8.7
Female	39	49.4	32	32	100	33	1.0	1	3.1	14	18	32	100	36	57.8	1 ^g 3.1
Females given olive oil	9	85.2	8	5	62.5	5	0.63	—	—	1	4	5	62.5	63	84.0	— —
Progeny treated with olive oil																
Male	20	88.0	19	10	52.6	13	0.7	3	15.8	4	4	8	42.1	57	84.0	5 ^h 26.3
Female	22	85.0	21	14	66.7	15	0.7	1	4.8	10	4	14	66.7	53	85.2	1 ⁱ 4.8
Untreated controls																
Male	54	94.2	53	38	71.7	42	0.8	4	7.5	22	12	34	64.2	31	87.4	8 ^j 15.1
Female	47	98.9	47	23	59.6	31	0.7	2	4.3	11	14	25	53.2	51	91.3	6 ^k 12.8

^aAll the animals taken in the experiment.^bSurvivors at the time the first tumor was observed.^cTumor-bearing animals.^dIn relation to the effective number of animals.^eLymphoma, salivary gland carcinoma.^fTwo liver-cell adenomas.^gUterine hemangioma.^hPapillary adenoma of urinary bladder, two liver-cell carcinomas, liver-cell adenoma, lymphoma.ⁱLymphoma.^jLymphoma, osteoma, three liver-cell carcinomas, two urinary bladder papillary adenomas, gland lacrimal adenoma.^kLymphoma, liver-cell carcinoma, gall bladder papillary adenoma, salivary gland cystadenoma, uterine hemangioma, uterine adenocarcinoma.

progeny of the styrene-treated mothers. At 20 weeks from the beginning of the experiment 50 % of the males and 20 % of the females had died, in spite of the fact that styrene administrations were suspended after 16 weeks because of obvious toxic effects. Neither the styrene nor olive oil treatments during pregnancy nor the continuous olive oil treatment for life had any effects on the survival rates of the other groups. The average age of death was 32 weeks for the males and 49 weeks for the females in the styrene-treated group, 88 and 85 weeks in the olive oil-treated and 94 and 99 weeks in the untreated controls.

Individual body weights were measured monthly and did not show considerable variations between the various groups. In the styrene-treated mice which died within the first 20 weeks from the beginning of the treatment, the most frequently observed lesions were multiple centrilobular necrosis of the liver, hypoplasia of the spleen, and severe congestion of the lungs. Extensive inflammatory reactions around the necrotic foci in the liver, bronchitis and peribronchitis were often seen in dying animals up to the 45th week from the beginning of the experiment. In animals which died later, the most frequent lesion was multiple abscess-like, round-shaped cavities in the liver, filled with polymorphonuclear leucocytes and surrounded by well-developed connective tissue capsule. Calcium deposits were also very numerous.

Tumors. Data on the tumor incidences of the O_{20} mice are summarized in table 2. No difference in the percentage of tumor-bearing animals was found between the females receiving a single administration of styrene in olive oil or olive oil alone, the progeny of olive oil-treated mothers receiving olive oil for life and in untreated controls.

An increased incidence of tumor-bearing animals was observed among the progeny of styrene-treated mothers receiving styrene for 16 weeks after weaning. The respective incidence was 89 % among the males and 100 % among the females of this group, in comparison with incidences of from 52 % to 71 % in the other groups

— this was solely in relation to an elevated incidence of lung tumors in styrene-treated animals. The difference in the percentage of animals with lung tumors between styrene-treated and olive oil-treated groups was statistically significant for both sexes ($p < 0.01$); however, the difference between the styrene-treated and untreated animals was statistically significant only for the females ($p < 0.001$) (males, $p = 0.1$).

In the styrene-treated group, lung tumors were observed in mice dying at a much earlier age than in the olive oil and untreated groups. The average age at death of mice with lung tumors was 49 and 58 weeks for the males and females of the styrene group, 84 and 85 weeks for the males and females of the olive oil group, and 87 and 91 weeks for the males and females of the untreated control, respectively. An exact count of the number of lung tumors per mouse was not made. Histologically, the lung tumors were either adenomas or adenocarcinomas, and the proportion between benign and malignant lung tumors did not appear to differ among the various groups.

The incidence of tumors occurring at sites other than the lung was higher in the untreated- and olive oil-treated mice than in the styrene-treated mice. This result could be clearly related to the much longer survival of mice in the first two groups as compared with mice in the styrene group.

C₅₇ Bl mice

The litter size and preweaning mortality of the progeny of C_{57} Bl females given single administration of either styrene or olive oil (control) during pregnancy were similar. The mortality of the animals weekly treated with doses of 300 mg/kg of styrene was not different from the mortality of olive oil-treated control animals, and their life-span was not shortened (table 3). Fifteen males and 12 females out of an initial number of 27 males and 27 females survived up to 120 weeks, when the experiment was terminated, at which time the survivors were killed. The body weights showed no considerable variations

Table 3. Survival rates of C₅₇ Bl mice treated with styrene and controls.

Group	Initial number	Number of survivors (weeks)											
		10	20	30	40	50	60	70	80	90	100	110	120
Females given styrene	15	15	15	15	15	14	13	13	12	11	9	7	4
Progeny treated weekly with styrene													
Males	27	27	27	27	27	27	26	25	24	21	18	15	15
Females	27	26	26	25	25	25	24	23	22	19	15	13	12
Females given olive oil	5	5	5	5	5	5	5	5	5	4	4	4	3
Progeny treated weekly with olive oil													
Males	12	12	12	12	12	12	12	12	11	10	10	7	7
Females	13	13	13	13	13	13	12	12	11	10	8	5	4
Untreated controls													
Males	51	51	51	51	51	50	50	50	49	46	40	36	33
Females	49	48	48	48	48	47	47	47	43	35	32	25	19

Table 4. Tumor incidence in C₅₇ Bl female mice treated with styrene on the 17th day of pregnancy, their progeny receiving weekly treatments for life, and controls.

Group	Initial number	Effective number ^a	TBA ^b		Average age at death (TBA ^b)	Number of tumors		Mice with more than one tumor		Animals with tumors							
			N	% ^c		N	Per mouse ^c	N	% ^c	Lymph		Lung		Liver		Others	
										N	% ^c	N	% ^c	N	% ^c	N	% ^c
Females given styrene	15	12	10	83.3	108.8	14	1.1	4	28.5	10	83.3	1	8.3	—	—	3 ^d	25.4
Progeny treated weekly with styrene																	
Males	27	24	12	50.0	114.8	14	0.6	3	12.5	9	37.5	1	4.2	3	12.5	1 ^e	4.2
Females	27	24	16	66.6	112.5	18	0.7	2	8.3	13	54.1	1	4.2	—	—	4 ^f	16.6
Females given olive oil	5	5	4	80.0	109.4	5	1.0	1	20.0	3	60.0	—	—	—	—	2 ^g	40.0
Progeny treated weekly with olive oil																	
Males	12	12	8	66.6	111.2	9	0.7	1	8.3	3	25.0	3	25.0	1	8.3	2 ^h	16.6
Females	13	13	6	46.1	90.8	7	0.5	1	7.7	5	38.4	1	7.7	—	—	1 ⁱ	7.7
Untreated controls																	
Males	51	47	20	42.5	111.1	22	0.47	2	4.2	13	27.6	5	10.6	1	2.1	3 ^j	6.4
Females	49	47	24	51.1	105.9	25	0.53	1	2.1	20	42.5	1	2.1	—	—	4 ^k	8.5

^aSurvivors at the time the first tumor was observed.

^bTumor-bearing animals.

^cIn relation to the effective number of animals.

^dJaw osteosarcoma, ovary granulosa-cell tumor, pituitary adenoma.

^eUrinary bladder papilloma.

^fTwo uterine sarcomas, spleen hemangioma, forestomach papilloma.

^gTwo pituitary adenomas.

^hHemangioendothelioma of the leg, s.c. hemangioma.

ⁱS.c. hemangioma.

^jForestomach papilloma, duodenum polyp, kidney adenocarcinoma.

^kTwo uterine sarcomas, adenoma of the lacrimal gland, ovary theca-cell tumor.

between styrene-treated and olive oil-treated animals.

Tumors. Cumulative data on tumor incidences in the styrene-treated, olive oil-treated and untreated controls are given in table 4. The percentage of tumor-bearing animals was similar in all the groups, except in females receiving a single styrene administration during pregnancy. However, the increased incidence observed in this group, mainly due to an increased incidence of lymphomas, was not statistically significant. Hepatocellular carcinomas were observed in three males receiving a weekly treatment of styrene, and one hepatocellular adenoma was observed in one olive oil-treated male and in one untreated male.

BD IV rats

The litter size in both the styrene- and olive oil-treated groups of BD IV rats was similar. The preweaning mortality of the progeny of females given a single administration of styrene of 1,350 mg/kg was 10 %, the corresponding mortality of olive oil-treated controls was 2.5 %. No considerable difference in survival rates was observed between the animals weekly treated with styrene and the those weekly treated with olive oil (table 5). There was no difference in body weight between styrene-treated and control animals.

Moderate congestion of lung and kidney and small necrotic foci in liver parenchyma were found in several animals which died at 50—60 weeks. The animals autopsied at 80—90 weeks and later showed no liver damage, but some lesions of forestomach (atrophy or local desquamation of epithelium, well-bordered necrotic areas with an inflammatory reaction of underlying tissues) and kidney (hyperplasia of pelvis epithelium) were frequently observed.

Tumors. Data on tumor incidences of the BD IV rats are summarized in table 6. The percentage of tumor-bearing animals was higher for females given a single administration of styrene during pregnancy than for any other group. The difference was

not statistically significant in comparison with females given a single administration of olive oil during pregnancy. A similar tumor incidence was observed in the styrene-treated progeny of females which received a single styrene administration and corresponding olive oil-treated controls. A few tumors occurring in the styrene-treated animals deserve some attention, however, since they were rarely seen in controls. Three stomach tumors, i.e., adenoma, fibrosarcoma, carcinosarcoma (the latter two with diffuse metastases) were observed in the styrene-treated animals, while one fibrosarcoma of the stomach was found in a female treated with olive oil. A single liver tumor (hepatocellular adenoma) was found in a female treated weekly with styrene. Three neurinomas, namely, of the heart, intestine, and *n. trigeminus*, were found in three styrene-treated rats. A meningioma, however, was observed in a control.

DISCUSSION

The administration of high weekly doses of styrene to O₂₀ mice resulted in a considerable shortening of the life-span due to the severe toxic effects of the chemical, mainly localized in the liver. No such toxic effects were observed in females receiving a single administration of styrene during pregnancy. In O₂₀ mice treated weekly with styrene, an increased incidence and earlier appearance of lung tumors were observed. In this strain of mice lung tumors occurred at a high incidence in untreated animals and the increased incidence observed in styrene-treated animals was significant for both sexes only if compared to the olive oil-treated mice. The incidence was statistically significant only for females if compared to the incidence observed for untreated mice. The proportion between benign and malignant lung tumors was similar in the various groups.

The tumor incidence in C₅₇ Bl mice treated with styrene was not statistically

different from that observed for controls, in spite of a slightly increased incidence of liver tumors.

In BD IV rats, treatment with styrene did not result in an incidence of tumors

different from that of controls receiving olive oil alone. There were, however, a few tumors in styrene-treated rats which were not observed in the control animals, namely, three neurogenic and three stom-

Table 5. Survival rates of BD IV rats treated with styrene and controls.

Group	Initial number	Number of survivors (weeks)											
		10	20	30	40	50	60	70	80	90	100	110	120
Females given styrene	21	21	21	21	21	20	20	20	20	20	20	14	10
Progeny treated weekly with styrene													
Males	73	72	71	71	71	71	69	67	62	58	39	20	8
Females	71	70	69	69	69	69	69	68	68	60	44	29	20
Females given olive oil	10	10	10	10	10	10	10	10	10	10	8	8	8
Progeny treated weekly with olive oil													
Males	36	36	36	36	36	36	36	35	34	31	26	25	14
Females	39	39	39	39	39	39	39	39	38	36	30	25	18

Table 6. Tumor incidence in BD IV female rats treated with styrene on the 17th day of pregnancy, its progeny receiving weekly treatments for life, and controls.

Group	Initial number	Effective number ^a	TBA ^b		Average age of TBA ^b at death	No of tumors		Animals with tumors											
								Lymph		Lung		Liver		Oral cavity		Stomach		Mammary gland	
			N	% ^c		N	Per rat ^c	N	% ^c	N	% ^c	N	% ^c	N	% ^c	N	% ^c	N	% ^c
Females given styrene	21	20	13	65.0	114.8	17	0.85	—	—	—	—	—	—	—	—	1	5.0	6	30
Progeny treated weekly with styrene																			
Males	73	54	5	9.1	110.0	5	0.1	1	1.9	1	1.9	—	—	—	—	—	—	—	3 ^e
Females	71	68	24	35.3	106.8	25	0.37	1	1.5	—	—	1	1.5	1	1.5	2	2.9	11	16.2
Females given olive oil	10	10	5	50.0	115.6	5	0.5	—	—	—	—	—	—	—	—	—	—	3	30
Progeny treated weekly with olive oil																			
Males	36	32	9	28.1	104.0	9	0.3	1	3.1	1	3.1	—	—	1	3.1	—	—	—	—
Females	39	35	17	48.5	109.3	21	0.6	1	2.9	—	—	—	—	1	2.9	1	2.9	15	42.9

^aSurvivors at time the first tumor was observed.

^bTumor-bearing animals.

^cIn relation to the effective number of animals.

^dNeurinoma of the intestine, s.c. fibroma, three uterine carcinomas, pheochromocytoma, three pituitary adenomas.

^eHeart neurinoma, neurinoma of the n. trigeminus, s.c. fibroma.

^fS.c. angiofibroma, uterine fibroadenoma, adrenal adenoma, vaginal sarcoma.

^gLeiomyosarcoma, adrenal adenoma.

^hOsteosarcoma, pituitary adenoma, mediastinal sarcoma, s.c. fibroma, meningioma, spleen hemangioma.

ach tumors. It may be of some relevance to note that lesions of the stomach were frequently observed in styrene-treated rats.

The increased incidence and early appearance of lung tumors could possibly indicate a carcinogenic effect for styrene in O_{20} mice. This experiment, however, has severe limitations, since the dose used was obviously very high, causing severe toxic effects and an early mortality. The findings of (a) a few tumors in styrene-treated rats which were rarely seen in controls and (b) a slightly increased incidence of liver tumors in C_{57} Bl mice treated with styrene cannot but raise some concern. Results from additional studies are needed before a final evaluation of the carcinogenicity of styrene in rodents can be made. Future research appears to be of particular importance in view of the recent results on the mutagenicity of styrene (3, 6).

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QUESTIONS AND ANSWERS

Questions to Dr. PONOMARKOV

- Dr. RANTANEN: The number of experimental animals was relatively small in all experimental groups, whereas the rate of spontaneous lung cancer was very high (about 80 % to 100 %). Do you think the number of animals is great enough for the detection of increased frequency of lung cancer cases after exposure to a weak carcinogen? Could the response be masked by a high rate of spontaneous cancer?
- Dr. PONOMARKOV: The increased incidence of lung tumors in O₂₀ mice treated weekly with styrene is statistically significant, and this difference would become even more evident if a larger number of animals were used.
- Dr. TORDOIR: The dosage given to the O₂₀ mice was 1,350 mg/kg per week. This seems to be a high dosage. Could you make a comparison of this dosage to a 5-d/8-h dosage in parts per million (inhalation)? Then a comparison could be made with actual occupational exposures.
- Dr. PONOMARKOV: Such a comparison has not been done.
- Prof. IKEDA: Could you let me know the malignancy of the lung tumors observed in the O₂₀ mice experiment?
- Dr. PONOMARKOV: The lung tumors observed in both styrene-treated and control O₂₀ mice were examined histologically. No difference in the proportion of benign and malignant tumors in different groups of animals was found.