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Subchronic Inhalation and Oral Toxicity of Hydrogenated Terphenyls in Rats[1]

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Subchronic Inhalation and Oral Toxicity of Hydrogenated Terphenyls in Rats. FARR, C. H., NAIR, R. S., DALY, I. W., TERRILL, J. B., AND JOHANNSEN, F. R. (1989). *Fundam. Appl. Toxicol.* 13, 558–567. The subchronic toxicity of a commercial blend of partially hydrogenated terphenyl was evaluated in rats by inhalation and oral routes of exposure. Animals were exposed to target concentrations of 0, 10, 100, or 500 mg/m^3 for 6 hr/day, 5 days/week or were offered diets daily with concentrations of 0, 50, 200, or 2000 ppm. Each study lasted approximately 14 weeks. The study designs included observations for clinical signs, body weights, ophthalmic exams, hematology and clinical chemistry, major organ weights, and gross and histopathology. No treatment-related effects were noted in the ophthalmic exams. Body weights were slightly depressed in high-dose males from the inhalation study and high-dose females in the dietary study. Liver and liver/body weights were increased in high-dose animals of both sexes and high- and mid-dose males in the dietary and inhalation studies, respectively. In the high-dose females of the dietary study, kidney and kidney/body weights were increased with increased adrenal and adrenal/body weights were also observed. No compound-related gross lesions nor pathological correlates to the organ weight changes were observed in either study. The no-adverse effect levels were considered to be 100 mg/m^3 and 200 ppm (15.9 mg/kg) for the inhalation and dietary studies, respectively. These data indicate that a wide margin of safety exists for hydrogenated terphenyl workplace exposure.

Terphenyls are produced commercially as ortho, meta, and para isomers. These materials are blended and partially hydrogenated (≅40%) to form the principal components in Therminol 66 (Santotherm 66) heat transfer fluid, Santosol 340 dye solvent, and HB-40 plasticizer (registered trademarks; Monsanto Co., St. Louis, MO).

The acute toxicity of partially hydrogenated terphenyls has been investigated; however, much of the published information relates to the testing of heat transfer fluids that were irradiated during use as coolants in nuclear reactors, and therefore subject to changes in composition. The nature of the irradiated material has not been characterized. This combination of data from irradiated and nonirradiated material may be confusing since the reader may not be aware of the differences in toxicity produced by the irradiated vs the nonirradiated materials. For example, Adamson and Weeks (1973) reported that the rat oral LD_{50} of nonirradiated material is 17,500 mg/kg while the rat oral LD_{50} for irradiated hydrogenated terphenyl is 6000 mg/kg.

Similar differences in toxicity have been observed in subchronic studies. In a 16-week oral gavage study, Adamson and Weeks (1973) noted severe and irreversible rat kidney lesions after exposure to 600 mg/kg/day of irradiated hydrogenated terphenyls compared to reversible kidney lesions seen after equivalent dosages of nonirradiated material. No lesions were observed with either material at a dosage of 250 mg/kg/day. The present TLV [registered trademark, American Conference of Governmental Industrial Hygienists (ACGIH)] and proposed Permissible Exposure Limit or PEL (Occupational Safety and Health Administration, 1988) of 0.5 ppm (≅5 mg/m^3) are based largely on irradiated material (ACGIH, 1986). The present studies were undertaken to develop comparative subchronic toxicity animal data by inhalation and oral routes of exposure to hydrogenated terphenyls as currently manufactured. The oral study provided a comparison to previous studies and the inhalation study provided a model for comparison to industrial exposure.

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METHODS

These studies were conducted in compliance with the provisions of the EPA Good Laboratory Practice Regulations (Environmental Protection Agency, 1984).

Test Material

Commercial grade Therminol 66 heat transfer fluid was supplied by Monsanto Co. Therminol 66 is primarily a mixture of terphenyl isomers (≅40% hydrogenated) with a typical ratio of approximately 1:5.4:2.6 for the *o*, *m*, and *p* isomers, respectively.

Animal Husbandry

Young, adult (6 weeks old in the oral study and 8 to 9 weeks old in the inhalation study) male and female Sprague–Dawley-derived (CD) rats (Charles River Breeding Laboratories, Wilmington, MA) were used in these studies. Animals were acclimated to the ambient laboratory conditions (temperature 67–76°F, relative humidity 30–65%, 12-hr light/dark cycle) for at least 14 days prior to study initiation. Rats, housed individually in stainless steel wire-bottomed cages, were provided Purina Certified Rodent Chow (Ralston-Purina Co., St. Louis, MO) and water *ad libitum* throughout the dietary study and during the nonexposure periods of the inhalation study.

Experimental Design

Oral study. Groups of 12 male and 12 female rats were assigned to each of four test groups at dietary target concentrations of 50, 200, and 2000 ppm. The fourth group received the basal diet only. Dietary exposure lasted for approximately 14 weeks.

Therminol 66 dietary concentrations were analyzed weekly throughout the study. Analyses for test article stability and homogeneity of the dietary admixtures were also completed. Aliquots of 10 or 20 g of dosed feed were shaken for 30 min in a total volume of 50 ml *n*-hexane. Five milliliters of high-dose extract was further diluted to 10 ml with *n*-hexane. To remove interfering substances, clean-up columns were prepared by adding approximately 0.5 g florisil to glass wool-plugged disposable pipets. An aliquot (2 ml of the control and low-dose and 1 ml of the mid- and high-dose levels) of the *n*-hexane extract was eluted through the columns with 9 ml *n*-hexane. The eluant was evaporated to dryness in a 40° water bath, and the residue was reconstituted with 1 ml *n*-hexane. Samples were injected into a gas chromatograph fitted with a flame ionization detector using a 6 ft × 2 mm i.d. glass column packed with 3% OV-17 on 80/100 Chromosorb WHP or equivalent. A temperature gradient program was run from 200 to 280°C at 15°C/min and the sum of the area of the generated peaks was integrated.

Inhalation study. Groups of 15 male and 15 female rats were assigned to each of four test groups. Three groups were exposed to target Therminol 66 concentrations of 10, 100, or 500 mg/m^3. The fourth group received house-supply air only. The 10 mg/m^3 atmosphere was regulated by placing the test material in a 10-cc syringe mounted to a syringe pump adjusted to flow at 0.8 ml/hr. The Therminol 66 was fed directly into an atomizing nozzle (¼ in. JSS nozzle with a No. 1A spray setup; Spray Systems Co., Wheaton, IL). Compressed air (back pressure 20 psi) was also passed through the atomizer. Metering pumps (Nupro, Willoughby, OH), feeding either a one-barrel Laskin nebulizer (back pressure 11 psi) or a two-barrel Laskin nebulizer (back pressure 20 psi), were used to generate the 100 and 500 mg/m^3 levels, respectively. Each generation apparatus containing test material was weighed before and after each exposure; weight differences before and after exposure divided by the total volume of air during exposure resulted in the nominal concentrations.

The Therminol 66 atmospheres entered the upper inlet portal of 1-m^3 glass and stainless-steel chambers fitted with pyramidal tops and bottoms. Dynamic exposures were maintained with calibrated air flow rates of approximately 200 liters/min for all chambers, including control. This flow rate provided one air change approximately every 5 min with 99% equilibrium times of approximately 23 min.

To characterize chamber atmospheres, samples were collected three times daily throughout the exposure period using Millipore filter holders with Whatman glass filter papers. Control samples were collected once daily. Single samples were taken at each collection time since preliminary studies indicated that the test article breakthrough to a second filter was less than 10% of the total sample. Sampling rates were approximately 10 liters/min lasting 40, 40, 10, and 3 min for control, 10, 100, and 500 mg/m^3 levels, respectively. The primary analyses were performed by *n*-hexane extraction of the terphenyls from the filters followed by gas chromatography using a flame ionization detector. The Therminol 66 samples were analyzed gravimetrically as a secondary, real-time assay. The uniformity of chamber distribution was analytically determined at each exposure level at least three times during the study.

Atmospheric particle size was measured 14 times during the study using a Delron DCI-6 cascade impactor. The mass distribution was calculated by determining the weight of the test material on each stage of the impactor to provide the mass median aerodynamic diameter with the accompanying geometric standard deviation.

Animal Observations and Procedures

All animals were observed daily for clinical signs of toxicity or mortality. Detailed physical examinations and individual body weight determinations were performed weekly. Food consumption was measured weekly in the feeding study. Ophthalmic examinations were performed in both studies by a veterinary ophthalmologist prior to the study initiation and just prior to termination. Blood samples were collected via puncture of the orbital sinus (retrobulbar venous plexus) from a set of 10 randomly selected animals/sex/dosage after 4 and 6 weeks of exposure for the dietary and inhalation studies, respectively. An additional blood sample was taken from each of the same animals at the study terminations. Clinical pathology parameters monitored in both studies included: hematology (erythrocyte count, hematocrit, hemoglobin, erythrocyte morphology, platelet count, and total and differential leukocyte counts) and clinical chemistry (total protein, albumin, globulin, total and direct bilirubin, glucose, cholesterol, creatinine, blood urea nitrogen, aspartate aminotransferase, and alanine aminotransferase). Specific clinical chemistry parameters evaluated in the dietary study included sodium, potassium, chloride, calcium, inorganic phosphorus, and γ glutamyl transpeptidase. In the inhalation study, additional clinical chemistry analyses included alkaline phosphatase, lactic dehydrogenase, and triglycerides.

Complete gross necropsies were performed on all animals at the study terminations. Animals were killed by exsanguination under ethyl ether anesthesia. Gross examinations were made of all organs, body cavities, cut surfaces, and external orifices and surfaces. Organ weights were recorded for adrenals, brain, kidney, liver, and testes in both studies. Lung and spleen weights were recorded in the inhalation study only. Microscopic examinations of hematoxylin and eosin-stained 6-μm sections were performed on the following tissues from all high-dose and control animals in both studies: adrenals, aorta (abdominal), bone (femur), bone marrow (sternum), brain (three sections, including frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons), esophagus, exorbital lacrimal glands, eyes (with contiguous Harderian glands), gonads (ovaries or testes and epididymides), heart, intestine (duodenum, jejunum, ileum, colon, cecum, and rectum), kidneys, liver (two sections from separate lobes), lungs (each lobe and mainstem bronchi), lymph nodes (mediastinal or peribronchial and mesenteric), mammary gland (right inguinal), nerve (sciatic with bicep femoris), pancreas, pituitary, prostate, salivary gland (submandibular), seminal vesicles, skin (with mammary gland), spinal cord (cervical, thoracic, and lumbar), spleen, stomach, thymic region, thyroid/parathyroid, trachea, urinary bladder, uterus (horns and cervix), gross lesions (including adjacent normal tissue), and tissue masses. The nasopharyngeal tissues (four sections through the head) were also examined in animals from the inhalation study. Lungs, liver, and kidneys were examined from all low- and mid-dose animals in the oral study.

Statistical Evaluations

Body weights, food consumption, absolute organ weights, organ to body weight ratios, hematology parameters, and clinical chemistry values were statistically analyzed. Initially, the equality of variances was determined with a Bartlett's test (Snedecor and Cochran, 1967). Group means with equal variances were further analyzed with a one-way analysis of variance (Snedecor and Cochran, 1967) followed by a Dunnett's test (Dunnett, 1955, 1964) if a significant F value was obtained. With unequal variances, a nonparametric procedure, the Kruskal–Wallis test (Hollander and Wolfe, 1973), was used to test the equality of means. Any differences in means were further evaluated with a Dunn summed rank test (Hollander and Wolfe, 1973) to determine which treatments differed from the control. Tests for trends among the dose levels were also performed. Standard linear regression methods were used for parametric data while the Jonckheere's Statistic (Hollander and Wolfe, 1973) was used to determine monotonic trends in nonparametric data. All tests were two-tailed with a minimum level of significance of $p < 0.05$.

RESULTS

Test Article Exposure

Oral study. The test material itself was deemed to be stable throughout the course of the study. The dosage mixtures were found to be stable and homogeneous. All dosed feed used in the study was within ± 10% of the target concentrations. Combined male and female dietary test article consumption (mean ± SD) was estimated to be 3.90 ± 0.25, 15.9 ± 0.91, and 156 ± 10.08 mg/kg/day for the dietary levels of 50, 200, and 2000 ppm, respectively.

Inhalation study. Therminol 66 chamber concentrations were considered to be homogeneous at each of the four sampling points on the exposure chambers. Average analytical concentrations (mean ± SD) were 11.4 ± 2.7, 98.6 ± 16.8, and 480 ± 46.9 mg/m^3. Samples taken from the control chamber showed no test material present at a detection limit of approximately 0.05 mg/m^3. Particle size determinations for the three test atmospheres indicated that the average mass median aerodynamic diameter ranged from 1.6 to 1.9 μm with accompanying geometric standard deviations of 1.8 to 2.0 μm. In all cases, the percentage of particles < 10 μm was ≧99%.

Animal Observations

All treated and control animals survived to the terminal euthanasia in the dietary study. Five animals died prior to terminal euthanasia in the inhalation study. A control female and a female in the 10 mg/m^3 exposure group died spontaneously. The exposed animal's death did not appear to be treatment related. Accidental deaths during blood collection included two females in the low-dose group and one female at the high dose.

Clinical signs, including alopecia, chromodacryorrhea, and lacrimation, were noted in both treated and control animals of the dietary study and were sporadic in frequency and duration. In the inhalation study, predominant clinical signs included lacrimation and rough coat in treated males and dried brown material about the face in treated females seen primarily in the mid- and high-dose animals. Minor ophthalmic lesions were found in both studies, but were not considered to be treatment related.

Dietary exposure to Therminol 66 resulted in a decreased weight gain (approximately to 7% less than controls) throughout the treatment period in high-dose females (Table 4). Treated males and other treated females had weight gains similar to their respective controls. Body weights of high-dose males exposed to Therminol 66 atmospheres were significantly reduced throughout most of the treatment period (Table 5). Terminal body weights in the high concentration group were 92% of controls. Body weights of other inhalation-treated males and treated females were considered unremarkable.

Food consumption in the dietary study was slightly lower in high-dose males and females when compared to controls during the first week of the study. Spillage from feeding jars was also noted during that period, most often in mid- and high-dose animals. Food consumption (g/day expressed as mean ± SD) was 81.6 ± 6.1, 79.0 ± 5.1, 79.5 ± 4.6, and 78.0 ± 5.0 for dietary levels of 0, 50, 200, and 2000 ppm, respectively. No other food consumption effects were noted during the treatment period.

Clinical Pathology

Hematology. Slight changes in hematological parameters were noted in the dietary study high-dose males at the 1-month interim sampling interval (Table 1). Significant ($p < 0.05$) decreases in mean hemoglobin concentration and hematocrit and erythrocyte counts with increased platelet counts were observed. No significant changes were seen in the remaining treated males and in the treated females. At the terminal bleeding period, only platelets in high-dose males were significantly higher than control values. The effects noted in the dietary study were not considered biologically significant because they were well within historical control values. Hematology indices were comparable in treated and control animals of both sexes at

TABLE 1

MEANS OF HEMATOLOGICAL PARAMETERS OF RATS EXPOSED TO HYDROGENATED TERPHENYLS FOR 13 WEEKS IN THE DIET

Target concentration (ppm)	Test week:	Hemoglobin (g/dl) 4	Hemoglobin (g/dl) 14	Hematocrit (%) 4	Hematocrit (%) 14	Erythrocyte count (10^6/mm^3) 4	Erythrocyte count (10^6/mm^3) 14	Platelets (10^5/mm^3) 4	Platelets (10^5/mm^3) 14
0 M		16.3 ± 0.2[a]	15.8 ± 0.6	44 ± 1	42 ± 1	7.21 ± 0.17	7.58 ± 0.23	10.62 ± 1.18	11.55 ± 1.59
F		15.4 ± 1.3	14.9 ± 0.8	42 ± 3	40 ± 2	6.69 ± 0.42	6.60 ± 0.39	10.91 ± 1.81	11.07 ± 2.72
10 M		15.8 ± 0.5	15.5 ± 0.5	42 ± 1	41 ± 2	7.05 ± 0.17	7.50 ± 0.31	10.54 ± 1.42	11.03 ± 1.87
F		16.0 ± 0.5	15.5 ± 1.5	43 ± 2	42 ± 4	6.95 ± 0.31	7.05 ± 0.71	10.03 ± 1.19	11.10 ± 1.61
100 M		15.9 ± 0.6	15.4 ± 1.1	43 ± 2	41 ± 2	7.16 ± 0.22	7.58 ± 0.55	11.14 ± 2.46	11.44 ± 1.51
F		16.1 ± 0.7	15.1 ± 0.7	44 ± 2	41 ± 2	6.92 ± 0.26	6.85 ± 0.44	12.75 ± 3.27	10.90 ± 1.45
500 M		15.5 ± 0.5**	15.0 ± 0.6	42 ± 1*	40 ± 2	6.87 ± 0.31**	7.28 ± 0.33	12.82 ± 1.63*	13.37 ± 1.21*
F		15.6 ± 0.6	14.7 ± 0.6	42 ± 2	40 ± 2	6.85 ± 0.36	6.78 ± 0.33	11.71 ± 1.96	11.11 ± 2.17

[a] Mean ± SD; $n = 10$.
* Statistically significant at $p \leq 0.05$.
** Statistically significant at $p \leq 0.01$.

both sampling periods in the inhalation study.

Clinical chemistry. Serum from animals in the dietary study indicated a statistically significant increase in cholesterol of high-dose males at the interim and terminal bleeding periods (Table 2). No significant clinical chemistry changes were observed for the low- and mid-dose males. Mid- and high-dose females showed statistically significant increases in calcium levels at the interim sampling period, with slight (not statistically significant) increases noted from terminal serum samples at these dosages. Glucose levels in high-dose females were significantly lower than control values at the 1-month sampling interval, with slightly lower (not statistically significant) levels reported for terminal samples from that group. Other treated female serum chemistry values were comparable to concurrent control values. The biological significance of these changes is doubtful since they remained in the range of historical control values.

Inhalation exposure to Therminol 66 produced several clinical chemistry changes (Table 3), including decreased aspartate aminotransferase and glucose levels in the high-dose females at Week 14 and increased total protein, albumin, and calcium levels in mid- and high-dose females at Week 14 when compared to control values. The blood urea nitrogen value for high-dose males was also increased at Week 14. Although these differences were statistically significant, the values remained in the range of historical controls and were thus not considered biologically significant.

Gross and Histopathology

None of the gross pathological observations described at necropsy in either study were considered to be treatment related, although some significant changes were observed in organ weights. In the dietary study, absolute kidney weights and kidney/body weight ratios were slightly higher in both

TABLE 2

MEANS OF CLINICAL CHEMISTRY PARAMETERS OF RATS EXPOSED TO HYDROGENATED TERPHENYLS FOR 13 WEEKS IN THE DIET

Target dietary concentration (ppm)	Test week:	Cholesterol (mg/dl) 4	Cholesterol (mg/dl) 14	Calcium (mg/dl) 4	Calcium (mg/dl) 14	Glucose (mg/dl) 4	Glucose (mg/dl) 14
0 M		55 ± 12[a]	77 ± 24	10.5 ± 0.3	10.6 ± 0.4	106 ± 14	131 ± 17
F		61 ± 15	83 ± 34	10.3 ± 0.4	10.5 ± 0.4	110 ± 20	118 ± 14
50 M		56 ± 11	80 ± 19	10.6 ± 0.5	10.7 ± 0.5	103 ± 16	133 ± 16
F		70 ± 13	90 ± 22	10.6 ± 0.3	10.8 ± 0.4	107 ± 10	120 ± 20
200 M		51 ± 14	77 ± 11	10.7 ± 0.4	10.6 ± 0.5	109 ± 18	147 ± 26
F		70 ± 13	93 ± 20	10.8 ± 0.2**	10.9 ± 0.5	106 ± 15	121 ± 23
2000 M		71 ± 16*	126 ± 33**	10.9 ± 0.4	11.0 ± 0.4	108 ± 27	137 ± 11
F		70 ± 13	84 ± 24	10.7 ± 0.3*	11.0 ± 0.5	92 ± 10*	105 ± 11

[a] Mean ± SD; $n = 10$.
* Statistically significant at $p \leq 0.05$.
** Statistically significant at $p \leq 0.01$.

male and female high-dose animals with statistically significant kidney/body weight ratio increases seen in the same animals (Table 4). These animals also showed significant increases in liver weights, liver/body weight ratios, and liver/brain weight ratios. High-dose females had increased adrenal and adrenal/body weight ratios. For the inhalation study, mean liver weights and liver/body weight ratios were increased above control values in all treated males in a dose-related manner; the changes in the high-dose group mean liver weight and in all liver/body weight ratios were statistically significant (Table 5). These slight changes were considered to be a normal adaptive response to xenobiotic exposure. The treated female liver weights were similar to their respective control values. All other organ weight and organ/body weight ratios were considered unremarkable.

Histopathological examinations in the dietary study revealed no test compound-related lesions and no pathological correlates to the increased kidney and liver weights. A spontaneous lesion in the kidneys of all male groups, including controls, was reported. This lesion consisted of small foci of hypertrophy and basophilia on the proximal tubular epithelium and was considered to represent young, regenerative cells. Similar lesions were found in only two females. The pathogenesis and biological significance of this lesion was not clarified; however, it was not considered to be treatment related. Histopathological examinations revealed no lesions related to the inhalation administration of Therminol 66 and no pathological correlates to the increased liver weights and differences in clinical chemistry values observed in that study.

DISCUSSION

The present TLV of 0.5 ppm (≅5 mg/m^3) for hydrogenated terphenyls and nonhydrogenated terphenyls is based on a combination of data from studies which used either irradiated or nonirradiated terphenyls. Coolant fluids previously used in nuclear reactors at the time the TLV was set differ substantially from currently used hydrogenated terphenyl formulations. One of the reactor coolants, Santowax OM mixed isomeric terphenyls

TABLE 3

MEANS OF CLINICAL CHEMISTRY PARAMETERS OF RATS EXPOSED TO HYDROGENATED TERPHENYLS FOR 13 WEEKS BY INHALATION

Target atmospheric concentration (mg/m^3)	Test week:	BUN[a] (mg/dl) 6	BUN[a] (mg/dl) 14	AST[b] (IU/liter) 6	AST[b] (IU/liter) 14	Glucose (mg/dl) 6	Glucose (mg/dl) 14	Total protein (g/dl) 6	Total protein (g/dl) 14	Albumin (g/dl) 6	Albumin (g/dl) 14	Calcium (mg/dl) 6	Calcium (mg/dl) 14
0 M		12.9 ± 1.8[c]	13 ± 1.5	107 ± 35	107 ± 28	128 ± 25	123 ± 21	5.6 ± 0.4	5.8 ± 0.3	3.5 ± 0.1	3.4 ± 0.2	9.8 ± 0.4	10.4 ± 0.2
F		15.1 ± 2.5	16.9 ± 4.8	95 ± 28	113 ± 51	131 ± 22	146 ± 23	5.9 ± 0.2	5.9 ± 0.3	3.6 ± 0.2	3.8 ± 0.2	10.3 ± 0.3	10.6 ± 0.4
10 M		12.6 ± 1.6	13.5 ± 1.8	104 ± 28	141 ± 71	130 ± 30	124 ± 18	5.5 ± 0.2	5.9 ± 0.5	3.5 ± 0.1	3.5 ± 0.2	9.8 ± 0.4	10.3 ± 0.4
F		15.6 ± 2.2	15.4 ± 1.6	91 ± 15	114 ± 31	133 ± 22	139 ± 22	6.0 ± 0.5	6.2 ± 0.3	3.7 ± 0.2	3.9 ± 0.2	10.4 ± 0.4	10.8 ± 0.4
100 M		13.9 ± 1.6	13.4 ± 0.9	88 ± 18	106 ± 25	140 ± 20	125 ± 16	5.4 ± 0.6	6.0 ± 0.4	5.0 ± 0.2	3.6 ± 0.2	10.1 ± 0.4	10.6 ± 0.4
F		14.3 ± 1.8	15.9 ± 3.1	84 ± 19	87 ± 18	127 ± 9	131 ± 19	6.1 ± 0.4	6.5 ± 0.4**	3.8 ± 0.2	4.1 ± 0.4*	10.7 ± 0.4	11.2 ± 0.5*
500 M		13.4 ± 1.6	15.8 ± 2.2**	81 ± 15	92 ± 15	124 ± 22	123 ± 24	5.7 ± 0.3	6.1 ± 0.5	3.7 ± 0.2	3.6 ± 0.2	10.2 ± 0.6	10.8 ± 0.4
F		14.5 ± 2.0	17.1 ± 1.6	86 ± 19	80 ± 12*	118 ± 21	117 ± 15*	6.1 ± 0.5	6.5 ± 0.4**	3.8 ± 0.2	4.2 ± 0.4**	10.5 ± 0.3	11.1 ± 0.5*

[a] Blood urea nitrogen.
[b] Aspartate aminotransferase.
[c] Mean ± SD; $n = 10$.
* Statistically significant at $p \leq 0.05$.
** Statistically significant at $p \leq 0.01$.

TABLE 4

ORGAN WEIGHTS IN RATS FOLLOWING DIETARY EXPOSURE TO HYDROGENATED TERPHENYLS FOR 13 WEEKS

Target dietary concentration (ppm)	0 M	0 F	50 M	50 F	200 M	200 F	2000 M	2000 F
Terminal body weight (g)	476 ± 49[a]	280 ± 26	503 ± 41	280 ± 36	486 ± 57	287 ± 30	464 ± 54	262 ± 17
Liver weight (g)	13.17 ± 1.46	7.52 ± 1.5	13.82 ± 1.42	7.52 ± 1.05	14.35 ± 2.38	7.82 ± 0.84	19.32 ± 2.49**	9.07 ± 1.16**
Liver to body weight ratio (g/100 g)	2.77 ± 0.09	2.68 ± 0.25	2.75 ± 0.15	2.69 ± 0.21	2.94 ± 0.21	2.69 ± 0.18	4.18 ± 0.42**	3.45 ± 0.29**
Kidney weight (g)	3.13 ± 0.40	1.81 ± 0.16	3.23 ± 0.35	1.91 ± 0.28	3.15 ± 0.32	1.98 ± 0.27	3.36 ± 0.38	2.02 ± 0.23
Kidney to body weight ratio (g/kg)	6.61 ± 0.81	6.63 ± 0.58	6.42 ± 0.58	6.84 ± 0.60	6.52 ± 0.58	6.90 ± 0.93	7.27 ± 0.59*	7.70 ± 0.52*
Liver to brain weight ratio (g/g)	6.26 ± 0.60	3.84 ± 0.55	6.59 ± 0.64	3.91 ± 0.59	6.85 ± 1.17	3.98 ± 0.40	9.35 ± 1.0**	4.68 ± 0.59**
Adrenal weight (mg)	53.2 ± 7.6	65.6 ± 1.0	52.8 ± 7.8	68.0 ± 1.4	53.3 ± 4.8	63.9 ± 8.8	54.4 ± 8.1	71.5 ± 9.1
Adrenal to body weight ratio (mg/10 g)	1.13 ± 0.21	2.34 ± 0.31	1.07 ± 0.22	2.43 ± 0.40	1.11 ± 0.17	2.28 ± 0.43	1.18 ± 0.18	2.73 ± 0.34*

[a] Mean ± SD; $n = 11$ or 12.
* Statistically significant at $p \leq 0.05$.
** Statistically significant at $p \leq 0.01$.

TABLE 5

LIVER WEIGHTS IN RATS FOLLOWING INHALATION EXPOSURE TO HYDROGENATED TERPHENYLS FOR 13 WEEKS

Target atmospheric concentration (mg/m^3)	0 M	0 F	10 M	10 F	100 M	100 F	500 M	500 F
Terminal body weight (g)	586 ± 33[a]	299 ± 25	570 ± 41	305 ± 19	594 ± 54	308 ± 33	543 ± 53*	298 ± 26
Liver weight (g)	18.62 ± 1.42	10.77 ± 1.30	19.76 ± 2.29	10.41 ± 1.02	20.74 ± 2.77	10.35 ± 1.20	21.60 ± 3.40*	11.04 ± 1.34
Liver to body weight ratio (g/100 g)	3.15 ± 0.16	3.61 ± 0.34	3.46 ± 0.25**	3.41 ± 0.23	3.49 ± 0.24**	3.37 ± 0.35	3.97 ± 0.37**	3.72 ± 0.33

[a] Mean ± SD; $n = 14$ or 15.
* Statistically significant at $p \leq 0.05$.
** Statistically significant at $p \leq 0.01$.

(registered trademark of Monsanto Co.), consisted of nonhydrogenated *o*- and *m*-terphenyl isomers with a maximum of 6% *p*-terphenyl isomer. Studies of irradiated Santowax OM are cited in the current documentation of TLVs (ACGIH, 1986), although such mixtures are no longer used as nuclear reactor coolant fluids in the United States. Since there are substantial differences in product chemistry and possible transformation products formed during irradiation, the use of irradiated terphenyl toxicity data is inappropriate for support of a TLV for hydrogenated terphenyls.

The results of the current inhalation and oral studies are considered to be more appropriate subchronic data for evaluating a workplace exposure level for hydrogenated terphenyl. If one makes several assumptions, viz, (1) 100% of the delivered dose was retained in the animals, (2) rat respiratory minute volume was approximately 250 ml (Dorato *et al.*, 1983), and (3) the average (male and female) body weight in this study was 333 g, it can be shown that the animals received similar body burdens of hydrogenated terphenyls in the two studies. The compound intake of approximately 2.96, 25.6, and 125 mg/kg/day was estimated for the average chamber concentrations in this study of 11.4, 98.6, and 480 mg/m^3, respectively. These estimates do not include test article exposure in the inhalation study via the dermal and oral (due to preening) routes associated with whole body inhalation exposure. In the oral study, combined male and female test article consumption was estimated to be 3.90, 15.9, and 156 mg/kg/day, which corresponds to the dietary levels of 50, 200, and 2000 ppm, respectively.

While a decrease of body weight gain was evident at the high dose in both studies, females were affected in the oral study and males were affected in the inhalation study. High-dose females also showed a significant decrease in food consumption during the early part of the the oral study which may have been related to palatability problems. Clinical signs of lacrimation, dried brown material about the face, and rough coat were associated with exposure at the mid- and high dose only in the inhalation study. While no hematological changes were noted in the inhalation study, hematological changes in the oral study were not considered biologically significant because they were well within the historical control values. Clinical chemistry changes were not consistent between studies and were not considered biologically significant because they were well within the historical ranges.

Increased liver weights and liver/body weight ratios were seen at the high-dose level in both sexes from the oral study and only in high-dose males from the inhalation study. Absolute kidney weights and kidney/body weight ratios were increased only in the high-dose animals of both sexes in the oral study. Gross and histopathological examinations revealed no lesions related to hydrogenated terphenyl administration in either study. In view of the lack of pathological observations, the significance of organ weight changes in high-dose animals from both the oral and inhalation studies is uncertain. Previous disposition studies after both oral and inhalation exposure suggest that hydrogenated terphenyls are localized in the liver and kidneys (Adamson and Furlong, 1974). Although no data on the effect of hydrogenated terphenyls on hepatic metabolism are available, *o*-, *m*-, and *p*-terphenyl isomers, each given as a single 100 mg/kg dose to rats 48 hr prior to euthanasia, resulted in significant increases of arylhydrocarbon hydroxylase and 7-ethoxyresorufin *o*-deethylase with all isomers and increased cytochrome P450 and cytochrome b_5 with the *o* and *m* isomers (Toftgard *et al.*, 1986). It is possible that the liver weight increases could be reflective of an adaptive response to insult. Therefore, the no adverse effect level in these studies is considered to be about 10 mg/kg/day in the dietary study and about 25 mg/kg day by inhalation.

A 70-kg human breathing 10 m^3/day at a TLV concentration of 5 mg/m^3 would be exposed to 0.7 mg hydrogenated terphenyl/kg body wt on a daily basis. This exposure level represents a safety factor of approximately 175-fold in comparing the lowest observable effect level of 125 mg/kg with the current TLV on a milligram per killigram basis. Comparison to the no observable effect level of approximately 25 mg/m^3 would provide a safety factor of about 36-fold. Human experience with hydrogenated terphenyls does not indicate a problem with respiratory, skin, or eye irritation during normal heat transfer operations at temperatures up to 650°F. Thus, results of these studies indicate that the present TLV of 5 mg/m^3 provides a wide margin of safety from subchronic effects for workplace exposure to nonirradiated hydrogenated terphenyls.

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21-2. 水素化テルフェニルのその他の毒性情報

他の毒性情報	[戸部ら：「水素化トリフェニールの毒性に関する研究」より引用] 急性毒性 経口 LD_{50} ラット（♂） ＝25000（21552～29000）mg/kg ラット（♀） ＝24000（20690～27840）mg/kg 反復投与試験 3ヶ月間 ラット混餌投与: 用量 ＝0.02、0.10、0.50、2.50 w/w% 死亡：2.50（4/10♂、1/10♀） 一般状態（削痩：2.50） 体重↓：0.10以上♂♀、摂餌量↓：0.10以上♀・2.50♂ 血液学的検査（RBC↓：0.10以上♂・0.50以上♀、 HGB↓・Hct↓：0.50以上♂0.02以上♂、 MCHC↓：0.50以上♀、 MCH↑：2.50♀、 PLT↑：0.10以上♂2.50♀ 骨髄検査（赤芽球↑・顆粒球↓：0.50以上♂♀） 血液生化学的検査（TP↓：2.50♂♀、A/G↑：0.10以上♂♀、 BUN↑：0.50以上♂・2.50♀、Glu↓：2.50♂♀、 TG↓：0.50以上♂・0.10以上♀、CRN↓：0.10♀、 Cho↑2.50♂、LAP↑：0.50以上♂、CHE↓：0.50♀、 γ-GTP↑：0.50♀、Ca↓：0.10以上♂、Pi↑：2.50♂♀、 Cl↑・Mg↑：2.50♂ 絶対重量（肝↑：0.50以上♂・0.10以上♀、卵巣↓：2.50♀） 相対重量（肝↑：0.10以上♂♀、卵巣↓：2.50♀） 回復（RBC↑、Hgb↓、MCHC↓、MCH↑、WBC↓、MVC↑、 TP↓、A/G↑、TG↓、CRN↓、Cho↓、Alp↑、Ca↓、Pi↑） 21ヶ月間 ラット混餌投与: 用量 ＝0.01、0.10、1.00 w/w% 死亡：あり（0.10以上） 一般状態（血涙・痩削↑：1.00♂♀） 体重↓：1.00♂♀ 血液学的検査♂18ヶ月、♀12ヶ月 （♂ RBC↓：0.01以上、Hgb↓・Hct↓：0.10、Plt↑：1.00 ♀ RBC↓・Hgb↓・Hct↓・MCV↓・Plt↑・WBC↑：1.00） 血液生化学的検査 18ヶ月 （Alb↑・BUN↑・TG↑・LAP↑：1.00♂♀、 A/G↑・Glu↓：0.10以上♂・1.00♀、 PL↓・TB↑・Alp↑・CHE↓・γ-GTP↑：1.00♀） 肝酵素活性 18ヶ月 （Alp↑・CHE↑・GOT↑・GPT↑・γ-GPT↑：1.00♀、 LAP↑：0.10以上♀・1.00♂、LDH-P↑：0.10以上♀） 絶対重量 18ヶ月（心↓・肺↓：1.00♂、肝↑：1.00♂♀、卵巣↓1.00♀） 相対重量 18ヶ月（脳↑：1.00♀、心↑：0.10♀・1.00♂、 肺↑：0.10以上♂・1.00♀、肝↑：0.10以上♀・1.00♂、 腎↑：0.10♂♀、脾↑：1.00♀、精巣↑：1.00♂、 副腎↑：0.10以上♂・1.00♀） 骨髄毒性に関する試験 ラット強制経口投与（1回及び連続4回） 1回投与（20g/kg） 骨髄有核細胞数：2日目及び4日目↓、4日目に最小値、6日以降回復 G/E比：4日目に最大、その後減少し、8日目から回復 連続投与（2.5, 5.0 g/kg） 骨髄有核細胞数：2日目及び4日目↓

	G/E 比：投与回数及び投与量に伴い増大
	[財団法人食品薬品安全センター試験検査成績書(1978)より引用] 変異原性試験 Ames 試験　陰性 純度記載なし TA1535, TA100, TA1537, TA98 -/+S9 mix 群　(0.1-100ul/plate)
	[Industrial BIO-TEST Laboratories Inc. No.663-04611 "Acute toxicity studies with Therm S 900"(1974)より引用] 急性毒性　純度記載なし 経口 LD_{50} ラット　= 23100 (17111～31185) mg/kg 経皮 LD_{50} ラット　= 6820 (4487～10366) mg/kg
	[Industrial BIO-TEST Laboratories Inc. No. 663-04611 "21-Day subacute heated vapor inhalation toxicity studies with Therm S 900"(1975)より引用] 反復投与試験 albino ﾗｯﾄ (0.7,1.1 mg/L/6h/day (吸入投与)) 5 日間/週×21 日間　純度記載なし 一般症状 (鼻炎・眼瞼下垂・身づくろい：0.7 以上) 絶対重量 (肝↑：1.1♂♀、肺↓：0.7♂) 相対重量 (対体重) (肝↑：1.1♂♀) 相対重量 (対脳重量) (肝↑：1.1♂♀、肺↓：0.7♂)
	[Industrial BIO-TEST laboratories, IBT No. 622-04610D "90-Day subacute oral toxicity studies with Therm S 900 in albino rats(1975)より引用] 反復投与試験 albino ﾗｯﾄ (100, 300, 1000ppm(混餌投与))　90 日間 純度記載なし 死亡 (0：1/15♀[採血中の死亡]、1000：2/15♀[採血中の死亡]) 絶対重量(肝↑：1000♂・100 以上♀) 相対重量(肝↑：1000♂・100 以上♀)
	[IUCLID (2000) より引用] 急性毒性 経口 LD_{50} ラット　= 10200 mg/kg、 = 17500 mg/kg、 > 24000 mg/kg、 > 10000 mg/kg マウス　= 12500 mg/kg 吸入 LC_{50} ラット　> 11.1 mg/L/4hr、 > 4.3 mg/L/4hr 経皮 LD_{50} ウサギ　= 6800 mg/kg、 > 2000 mg/kg 刺激性 ウサギ　皮膚　中程度の刺激性あり (2 報) 刺激性なし (1 報) ウサギ　眼　刺激性なし (2 報) 感作性 ヒト (パッチテスト)　感作性なし (2 報) 反復投与試験 Charles River COBS ﾗｯﾄ(0.01, 0.05, 0.25 mg/L/6h/day(吸入投与)) 30 日間 (5days/w) 純度記載なし NOAEC = 0.25 mg/L/6h/day (活動性↓) SD ﾗｯﾄ (0.01, 0.1, 0.5 mg/L/6h/day(吸入投与)) 90 日間 (5days/w) 純度記載なし NOAEC = 0.1 mg/L/6h/day (肝重量↑♂、流涙、色素涙) LOAEC = 0.5 mg/L/6h/day (肝重量↑♂、体重↓♂、流涙、色素涙) 系統未記載ﾗｯﾄ(0.01, 0.05 mg/L/6h/day(吸入投与))　182 日間 (5days/w) 純度記載なし

NOAEC = 0.01 mg/L/6h/day（影響なし）
LOAEC = 0.05 mg/L/6h/day（肝重量↑♂、血液生化学的検査項目（Glu↓・BUN↓♂・SAP↑♂・SGOT↑♂・SGOT↓♀・SGPT↑♂））
（試験の信頼性に問題を示唆するコメントあり）

系統未記載ﾏｳｽ（0.5 mg/L/7h/day(吸入投与)）≧4 日間　純度記載なし
NOAEC = 0.5 mg/L/7h/day（タイプ 2 肺胞細胞のミトコンドリアの空胞化増加が観察されたが、曝露終了 42 日目には回復）

系統未記載ﾏｳｽ（0.5 mg/L/7h/day(吸入投与)）≧8 日間　純度記載なし
NOAEC = 0.5 mg/L/7h/day（タイプ 2 肺胞細胞のミトコンドリアの空胞化増加が観察されたが、曝露終了 42 日目には回復）

系統未記載ﾊﾑｽﾀｰ（0.01, 0.05 mg/L/6h/day(5days/w)(吸入投与)) 182 日間 純度記載なし
NOAEC = 0.01 mg/L/6h/day（脾重量↓）
LOAEC = 0.05 mg/L/6h/day
（血液学的及び血液生化学的検査項目（Hgb↓・Glu↓♂・Glu↑♀・SAP↑♀））
（試験の信頼性に問題を示唆するコメントあり）

Macacsa Fascicularis ｻﾙ（0.01, 0.05 mg/L/6h/day（5days/w）(吸入投与)) 182 日間 純度記載なし
NOAEC = 0.01 mg/L/6h/day（死亡↑♂）
LOAEC = 0.05 mg/L/6h/day（血液学的及び血液生化学的検査項目（RBC↑♀・WBC↓♂・BUN↑♀・SAP↑♀））
（試験の信頼性に問題を示唆するコメントあり）

SD ﾗｯﾄ （1000, 5000, 10000, 20000ppm (混餌投与)) 14 日間 純度記載なし
(60, 300, 600, 1200 mg/kg/day 相当)
NOAEL = 60 mg/kg/day（肝重量↑）
LOAEL = 300 mg/kg/day
（体重↓♀、肝重量↑、脾重量↑♀、肝剖検（肥大・変色等）

Albino ﾗｯﾄ （1000ppm(混餌投与)) 42 日間 純度記載なし
(60 mg/kg/day 相当)
NOAEL = 60 mg/kg/day（影響なし）

Albino ﾗｯﾄ（100,300,1000ppm(混餌投与)）90 日間　純度記載なし
(6, 18, 60 mg/kg/day 相当)
NOAEL = 18 mg/kg/day（影響なし）
LOAEL = 60 mg/kg/day（死亡↑♀、臓器重量↑：肝♀・腎♀・脳♀）

SD ﾗｯﾄ(50, 200, 2000ppm(混餌投与)) 90 日間　純度記載なし
(3, 12, 120 mg/kg/day 相当)
NOAEL = 12 mg/kg/day（肝重量↑♂）
LOAEL = 120 mg/kg/day（体重↓♀、血液生化学的検査項目（Hgb↓♂・Hct↓♂・RBC↓♂・Plt↑♂）、臓器重量↑（肝臓・腎臓・副腎♀））

Leghorn ﾒﾝﾄﾞﾘ （100, 500 ppm(混餌投与)) 30 日間 純度記載なし
NOAEL = 500 ppm（影響なし）

Carworth ﾗｯﾄ(1.004, 4.016, 10.16 mg/kg/day(経口投与)) 70 日間 (5days/w) 純度記載なし
NOAEL < 1.004 mg/kg/day
LOAEL = 1.004 mg/kg/day（病理組織学的所見：肝－肝細胞の変性及び壊死・腎－尿細管上皮細胞の変性及び壊死・脳－変性）

JAX ﾏｳｽ　(20～2000 mg/kg/day(経口投与)) 112 日間（1,2 回/週）純度記載なし
NOAEL = 600 mg/kg/day（腎－間質性腎炎、可逆性）
LOAEL = 1200 mg/kg/day（腎－間質性腎炎）

系統未記載ｳｻｷﾞ（1.004, 4.016, 10.04 mg/kg/day（5days/w）(経口投与)) 35 日間　純度記載なし
NOAEL = 1.004 mg/kg/day
LOAEL = 4.016 mg/kg/day（死亡↑、体重↓、摂餌量↓、病理組織学的所見：肝－肝細胞の変性及び壊死・腎－尿細管上皮細胞の変性及び壊

死・脳－変性）
New Zealand white ｳｻｷﾞ（125, 500, 2000 mg/kg/6h/day（5days/w）（経皮投与））
21 日間　純度記載なし
NOAEL = 2000 mg/kg/6h/day（全身性の影響なし）
遺伝毒性試験
Ames 試験
陰性
純度記載なし、　溶媒（DMSO）
TA1535, TA1538, TA100, TA98, TA1537
-/+S9mix 群：10000μg/plate、細胞毒性なし
陰性
純度記載なし、　溶媒：不明
TA1535, TA1538, TA100, TA98, TA1537
-/+S9mix 群：10μl/plate
（100μl/plate まで細胞毒性なし）
HGRPT アッセイ：陰性
純度記載なし、溶媒：不明
CHO 細胞
-/+S9mix 群：300μg/ml
（1600μg/ml まで細胞毒性なし）
In vitro UDS 試験：陰性
純度記載なし、　溶媒（アセトン）
肝細胞
-/+S9mix 群：1000μg/ml
（5000μg/ml まで細胞毒性なし）
In vivo 細胞遺伝学的試験：陰性
純度記載なし、　溶媒（コーン油）
ラット、腹腔内投与、250, 1250, 2500 mg/kg
発がん性試験
Balb/c ﾏｳｽ・PLA ﾏｳｽ（50 mg/week（経皮投与））37 週間（週一回皮膚塗布）純度記載なし
影響なし
生殖発生毒性試験
Leghorn ﾒﾝﾄﾞﾘ（30, 100, 300 ppm(混餌投与)）　90 日間 純度記載なし
母毒性及び F1 毒性の NOAEL = 300 ppm（産卵下がるが曝露終了後回復）
SD ﾗｯﾄ（30, 100, 300, 1000 ppm(混餌投与)）　2 世代 純度記載なし
投与期間：～分娩後 21 日まで
親動物に対する NOAEL = 1000 ppm（62 mg/kg/day 相当）（体重↓♂）
F1 に対する NOAEL = 1000 ppm（63 mg/kg/day 相当）（体重↓♀）
SD ﾗｯﾄ（25, 250, 500, 1000, 2000 mg/kg/day(経口投与)）妊娠 6～15 日 純度記載なし
母獣毒性の NOAEL = 250 mg/kg/day（500 で摂餌量↓）
催奇形性の NOAEL = 1000 mg/kg/day（2000 で胚死亡・胎児の体重↓）
SD ﾗｯﾄ（125, 500, 1500 mg/kg/day(経口投与)）妊娠 6～15 日 純度記載なし
母獣毒性の NOAEL = 125 mg/kg/day（500 で摂餌量↓）
催奇形性の NOAEL = 500 mg/kg/day（1500 で胎児の体重↓・胎児骨格奇形↑、骨格変異↑）