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Summary information of human health hazard assessment of existing chemical substances（V）

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The Japanese Chemical Substances Control Law states information collected by the Japanese Ministry of Health, Labour and Welfare（MHLW）on the hazards to human health associated with existing chemical substances. Here, we review the hazard information collected by the MHLW, including data on acute toxicity, repeated-dose toxicity, genotoxicity, and reproduction/developmental toxicity. We present a dossier comprising a collection of study data with a detailed summary of the methods, results, and conclusions included in each study, using the International Uniform Chemical Information Database（IUCLID）to clarify and evaluate the validity of each study. In this fifth annual report, we summarize the hazard information related to the potential effects on human health of five chemical substances: perfluorooctane（CAS: 307-34-6）, azoic CC5（CAS: 91-96-3）, triallylamine（CAS: 102-70-5）, *N*-ethyl-1-aminonaphthalene（CAS: 118-44-5）, and 4,4'-methylenebis（2,6-di-*tert*-butylphenol）（CAS: 118-82-1）. The IUCLID dossiers created for these five chemical substances will be available at the Japan Existing Chemical Database. Information regarding hazards to human health of other existing chemical substances will be provided on a regular basis using the same methodology and website as it becomes available.

Keywords: hazard assessment, human health, IUCLID, dossier, JECDB

Introduction

The Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. within the Chemical Substances Control Law（CSCL）came into effect in 1973 to prevent environmental pollution by chemical substances that pose a risk to human health or the environment in Japan. The Japanese CSCL requires information on the hazards to human health associated with existing chemical substances to be collected and assessed by the Ministry of Health, Labour and Welfare（MHLW）[1], including data on acute toxicity, repeated-dose toxicity, genotoxicity, and reproduction/development toxicity. To date, the MHLW has collected information on around 450 existing chemical substances. Among these, initial assessment documents for approximately 200 substances had been submitted from Japan to the OECD High Production Volume Chemicals Programme or OECD Cooperative Chemicals Assessment Programme from the 1990s to 2013 and had been internationally approved. These assessment documents are publicly available at https://hpvchemicals.oecd.org/ui/Search.aspx. We have gradually assessed the hazard information of the remaining existing chemical substances and created a dossier using the International Uniform Chemical Information Database（IUCLID）[2] a leading database in risk assessment of chemical substances, to process the results of each study and evaluate their validity. Each dossier was composed of data from all studies, including a detailed summary of the methods, results, and conclusions for each. The IUCLID dossiers are available internationally via the Japan Existing Chemical Database（JECDB）,

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Table 1. List of the 15 substances available in the Japan Existing Chemical Database

CAS Number	Substance name
638-16-4	1, 3, 5-Triazine-2, 4, 6 (1H, 3H, 5H)-trithione
2579-20-6	1, 3-Cyclohexanedimethanamine
6842-15-5	1-Propene, tetramer
31127-54-5	2, 3, 4, 4'-Tetrahydroxybenzophenone
119-33-5	2-Nitro-*p*-cresol
59-50-7	4-Chloro-*m*-cresol
104-88-1	4-Chlorobenzaldehyde
122-01-0	4-Chlorobenzoyl chloride
98-10-2	Benzenesulfonamide
70974-33-3	Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt
542-18-7	Chlorocyclohexane
4904-61-4	Cyclododeca-1, 5, 9-triene
3012-65-5	Diammonium hydrogen 2-hydroxypropane-1, 2, 3-tricarboxylate
37353-75-6	Poly [oxy (methyl-1, 2-ethanediyl)], alpha,alpha'- [(1-methylethylidene) di-4, 1-phenylene] bis [omega-hydroxy-
89-05-4	Benzene-1, 2, 4, 5-tetracarboxylic

and are accessible at http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp[3]. IUCLID dossiers for 15 existing chemical substances are currently available from JECDB (Table 1). Summaries of hazard assessments were also reported annually[4-7]. The same methodology and website will be used to provide information on hazards to human health for existing chemical substances on a regular basis as it becomes available.

These initiatives will provide global access to meaningful toxicity information, avoiding duplication of assessment work performed by other programs or countries. Information sharing can also prevent unnecessary animal studies. Therefore, we consider our initiative a significant contribution to the challenges faced worldwide in the field of risk assessment of chemical substances.

In this fifth report, we present summary hazard information for the following five chemical substances: perfluorooctane (CAS: 307-34-6), azoic CC5 (CAS: 91-96-3), triallylamine (CAS: 102-70-5), *N*-ethyl-1-aminonaphthalene (CAS: 118-44-5), and 4,4'-methylenebis (2,6-di-*tert*-butylphenol) (CAS: 118-82-1). No toxicological studies on these chemical substances were performed previously.

(1) Perfluorooctane (CAS: 307-34-6)

A combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test was performed in accordance with OECD test guideline (TG) 422. Male and female rats (12 animals/sex/dose) received perfluorooctane via oral gavage at doses of 0 [vehicle: 1% (w/v) sodium carboxymethylcellulose solution and 1% (v/v) Tween 80], 100, 300, and 1,000 mg/kg body weight (bw)/day. Males were treated with perfluorooctane for 42 days in males, including a 14-day premating period and a subsequent mating period, while females were treated for 41–53 days, including 14-day premating, mating, and gestation periods, until lactation day 4. Of the 12 males treated with 0 and 1,000 mg/kg bw/day, five were

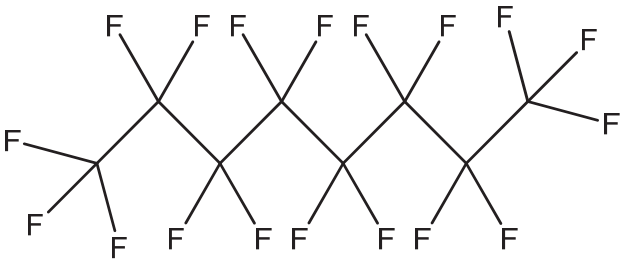

Fig. 1. Chemical structure of perfluorooctane (CAS: 307-34-6)

assigned as a recovery group. Five additional females treated with 0 and 1,000 mg/kg bw/day were assigned as a satellite group and treated with perfluorooctane for 42 days, without mating, and examined after a 14-day recovery period.

There were no deaths and no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, hematology, blood chemistry, organ weight, or gross and histopathological findings as a result of treatment in any of the dose groups for both sexes at the end of the treatment and recovery periods. The NOAEL for the repeated-dose toxicity of perfluorooctane was determined to be 1,000 mg/kg bw/day (the highest dose tested) in rats.

A bacterial reverse mutation assay using *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537, and *Escherichia coli* WP2*uvrA* (OECD TG 471) showed negative results for perfluorooctane, with or without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473) was also negative, both with and without metabolic activation. These results revealed that perfluorooctane is nongenotoxic *in vitro*.

In the combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test (OECD TG 422) described above, no toxicity was observed in reproduction and development up to the highest dose. The NOAEL for the toxicity of perfluorooctane to rat reproduction and development was determined to be 1,000 mg/kg bw/day (the highest dose tested).

(2) Azoic CC5 (CAS: 91-96-3)

The repeated-dose toxicity of azoic CC5 was evaluated in rats according to the OECD TG 407. Male and female rats (6 or 12 animals/sex/dose) were

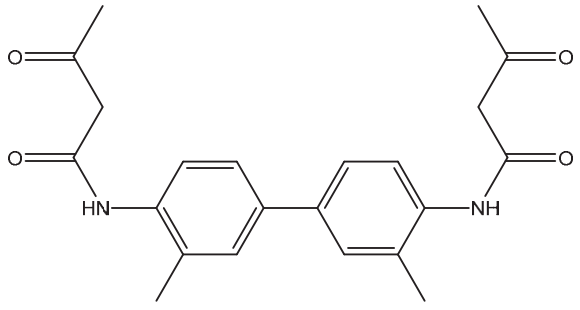

Fig. 2. Chemical structure of azoic CC 5 (CAS: 91-96-3)

treated with 0 [vehicle: 0.5% (w/v) methylcellulose solution], 8, 40, 200, and 1000 mg/kg bw/day azoic CC5 for 28 days. Six of the 12 animals/sex receiving 0 and 1,000 mg/kg bw/day were selected for a 14-day recoverygroup.

No treatment-related deaths were observed for either sex. For both sexes, decreased food consumption, body weight, and body weight gain were observed in the groups receiving ≥40 mg/kg bw/day. Water intake was decreased in males receiving ≥40 mg/kg bw/day as well as females receiving 1,000 mg/kg bw/day. Urine volume was decreased in males receiving 1,000 mg/kg bw/day. Blood chemistry analysis showed increased total cholesterol and phospholipid levels in both sexes treated with 1000 mg/kg bw/day. The relative weight of the liver was increased in males receiving ≥40 mg/kg bw/day and females receiving ≥ 200 mg/kg bw/day. Histopathological analysis revealed centrilobular hepatocellular hypertrophy in both sexes treated with ≥40 mg/kg bw/day. Following withdrawal of treatment, the changes observed during or at the end of the administration period were no longer observed, and were thus reversible. Based on the effects in the liver observed at 40 mg/kg bw/day, the NOAEL for the repeated-dose toxicity of azoic CC5 in rats was determined to be 8 mg/kg bw/day.

A bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537, and *E. coli* WP2*uvrA* (OECD TG 471) showed positive results for *S. typhimurium* TA100 and TA98 with metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473) also showed positive results for polyploidy without metabolic activation. Based on these findings, azoic CC5 was considered to be genotoxic *in vitro*.

The reproductive and developmental toxicity of azoic CC5 was evaluated in a reproduction/developmental toxicity screening test in rats (OECD TG 421). In this study, azoic CC5 was administered via oral gavage at doses of 0 [vehicle: 0.5% (w/v) methylcellulose solution], 2.5, 10, and 40 mg/kg bw/day. Males (12/dose) were treated for 42 days, including a 14-day premating period and subsequent mating period, while females (12/dose) were treated for 40–49 days, including 14-day premating, mating, and gestation periods, until lactation day 3.

No deaths were observed due to treatment in either

sex. Decreased food consumption, body weight, and body weight gain were observed in males treated with 40 mg/kg bw/day and females treated with ≥10 mg/kg bw/day. At doses of ≥2.5 mg/kg bw/day, body weight gain and body weight decreased in females during the lactation period. An increased relative liver weight was observed in males treated with ≥10 mg/kg bw/day and females treated with 40 mg/kg bw/day, and centrilobular hepatocellular hypertrophy was observed in males treated with 40 mg/kg bw/day. No changes were observed in reproductive organs, and fertility was not also affected by azoic CC5 treatment up to 40 mg/kg bw/day. Decreased body weight was observed in male and female pups at 40 mg/kg bw/day. A NOAEL could not be identified, as decreases were observed in body weight gain or body weight in females during the lactation period at all doses. The LOAEL of the reproductive/developmental toxicity was determined to be 2.5 mg/kg bw/day.

(3) Triallylamine (CAS: 102-70-5)

The repeated-dose toxicity of triallylamine was evaluated in rats according to the OECD TG 407. Male and female rats (6 or 12 animals/sex/dose) were treated with triallylamine via oral gavage for 28 days at 0 (vehicle: corn oil), 6, 25, and 100 mg/kg bw/day. Six of the 12 animals/sex receiving 0 and 100 mg/kg bw/day were assigned to a 14-day recovery group prior to sacrifice.

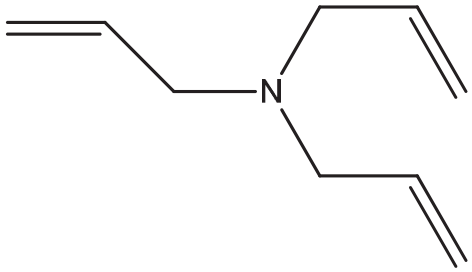

Fig. 3. Chemical structure of triallylamine (CAS: 102-70-5)

No deaths were observed in either sex. Decreased salivation and locomotor activity were observed at the beginning of the dosing period at the highest dose in both sexes. Hind limb grip strength decreased in males treated with 100 mg/kg bw/day. Body weight and body weight gain were decreased in both sexes treated with 100 mg/kg bw/day. Food consumption was decreased in both sexes treated with ≥25 mg/kg bw/day. Water intake was increased in males receiving 25 and 100 mg/kg bw/day. Treatment with 100 mg/kg bw/day led to increased urine volume in males and decreased osmolality in both sexes, and positive results for calcium oxalate crystals tended to increase in the urine sediment examination in both sexes. Blood chemistry analysis showed decreased triglyceride levels in males receiving 25 and 100 mg/kg bw/day, but increased levels in females receiving 100 mg/kg bw/day. The relative weight of the kidney was increased, without histopathological changes, in males receiving 100 mg/kg bw/day. In females, the relative weight of the liver was increased at 25 and 100 mg/kg bw/day, while the absolute weight of the liver was increased in both sexes treated with 100 mg/kg bw/day. Histopathological examination of the liver showed centrilobular hepatocellular hypertrophy in both sexes receiving ≥25 mg/kg bw/day. Changes due to triallylamine treatment observed during or at the end of the 14-day recovery period recovered, with some exceptions. Body weight remained decreased during the recovery period in females treated with 100 mg/kg bw/day, and centrilobular hepatocellular hypertrophy was observed in males treated with 100 mg/kg bw/day. Based on the histopathological changes in the liver in the 25 mg/kg bw/day group, the NOAEL for repeated-dose of triallylamine was determined to be 6 mg/kg bw/day in rats.

A bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537, and *E. coli* WP2*uvrA*/pKM101 (OECD TG 471) for triallylamine showed weak-positive or positive results for TA100 and TA1535 without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473) showed that triallylamine was equivocal (weakly positive) for numerical aberration with and without metabolic activation, and positive for structural aberration with metabolic activation. Based on the positive results in both studies, triallylamine was considered genotoxic *in vitro*.

The reproductive and developmental toxicity of triallylamine was investigated in accordance with a reproduction/developmental toxicity screening test (OECD TG 421) in rats. Triallylamine was administered via oral gavage at doses of 0 (vehicle: corn oil), 6, 25, or 100 mg/kg bw/day. Males (12/dose)

were treated for 30 days, including a 14-day premating period and a subsequent mating period. Females (12/dose) were treated for 40–47 days, including 14-day premating, mating, and gestation periods, until lactation day 3.

There were no treatment-related deaths in either sex. Decreased locomotor activity, salivation, and lacrimation were observed at the beginning of the treatment period in both sexes treated with ≥25 mg/kg bw/day. Body weight gain was decreased in males treated with ≥6 mg/kg bw/day and females treated with ≥25 mg/kg bw/day. Food consumption decreased in both sexes treated with ≥25 mg/kg bw/day. Similar to the 28-day repeated-dose toxicity study described above, treatment with 25 mg/kg bw/day triallylamine showed effects in the liver and increased organ weights with histopathological changes. No effects on reproductive organs and fertility were observed following triallylamine treatment. Analysis of developmental toxicity showed decreased body weight in male pups in the 100 mg/kg bw/day group and a tendency to decrease in male pups at 25 mg/kg bw/day group and female pups at 25 and 100 mg/kg bw/day groups on postnatal day (PND) 4. Based on the effects in body weight of pups at 25 mg/kg bw/day group, the NOAEL of reproductive and developmental toxicity was considered to be 6 mg/kg bw/day.

(4) *N*-ethyl-1-aminonaphthalene (CAS: 118-44-5)

A 28-day oral toxicity study (OECD TG407) of *N*-ethyl-1-aminonaphthalene was conducted in rats (6 or 12/dose/sex). Dose levels were set at 0 (corn oil), 12, 60, and 300 mg/kg bw/day. Treatment was withdrawn for 2 weeks after the end of the administration period to examine the reversibility of the toxic effects, using six animals/sex in the control and 300 mg/kg bw/day groups.

One female in the 300 mg/kg bw/day group died on day 4 of treatment after showing decreased locomotor activity, soft feces, and brown urine. Clinical observation of the survivors revealed brown urine in the males and females in the ≥60 mg/kg bw/day groups, and soft feces in males and females in the 300 mg/kg bw/day group. Low motor activity was observed in males in the 300 mg/kg bw/day group. Body weight and food consumption in both sexes and body weight gain in males were decreased in the 300 mg/kg bw/day group. High values were observed for water intake and urine volume, and low values were observed for osmolality in both sexes at 300 mg/kg bw/day. Hematological toxicity, low values for red blood cell count, hemoglobin, and hematocrit, and/or a high values for reticulocyte percentage, were observed at doses of ≥60 mg/kg bw/day in females and 300 mg/kg bw/day in males.

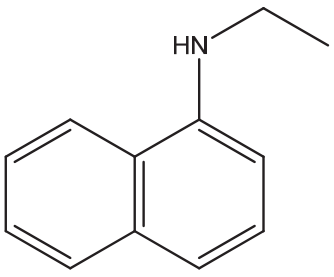

Fig. 4. Chemical structure of *N*-ethyl-1-aminonaphthalene (CAS: 118-44-5)

Blood chemistry analysis showed high levels of total cholesterol and phospholipid compared with the control group in both sexes treated with 60 mg/kg bw/day. Treatment with 300 mg/kg bw/day led to low levels of creatinine in both sexes, high levels of alanine transaminase and lactate dehydrogenase in males, and a high levels of total protein in females compared with the control groups. The relative weight of the kidney was increased in both sexes at 300 mg/kg bw/day. Microscopic evaluation showed increased mild extramedullary hematopoiesis in males, and hemosiderin deposition (slight/mild Berlin-blue positive granules) in the spleens of both sexes treated with ≥60 mg/kg bw/day. Hypertrophy of centrilobular hepatocytes of bile duct epithelial cells in the liver was observed in males of the 60 and 300 mg/kg bw/day groups and in females of the 300 mg/kg bw/day group. Increased erythropoiesis was observed in the femurs of males and females and in the sternum in males treated with 300 mg/kg bw/day. These changes were either reduced or no longer observed following withdrawal of treatment. The NOAEL of *N*-ethyl-1-aminonaphthalene was considered to be 12 mg/kg bw/day due to the results of hematological toxicity with related histopathological changes in the spleen observed with 60 mg/kg bw/day.

A bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537, and *E. coli* WP2*uvrA* (OECD TG 471) showed negative results for *N*-ethyl-1-aminonaphthalene with or

without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473) showed that *N*-ethyl-1-aminonaphthalene induced structural chromosome aberration with metabolic activation, but showed no potential to induce numerical chromosome aberration (polyploidy). A *gpt* delta transgenic mouse assay (OECD TG 488) showed negative results in the liver, bone marrow, and testes up to the maximum tolerated dose. These findings indicated that *N*-ethyl-1-aminonaphthalene is nonmutagenic *in vitro* and *in vivo*, but clastogenic *in vitro*.

The reproductive and developmental toxicity of *N*-ethyl-1-aminonaphthalene was investigated in rats in accordance with the OECD TG 421 reproductive/developmental toxicity screening test. Rats were treated with *N*-ethyl-1-aminonaphthalene via oral gavage at doses of 0 (vehicle: corn oil), 12, 60, or 300 (reduced to 150) mg/kg bw/day. Males (12/dose) were treated for 42 days, including a 14-day premating period and a subsequent mating period, while females (12/dose) were treated over a 14-day premating, mating, gestation, and lactation period (up to on day 3 of lactation). In the highest dose group, eight males and five females died during the premating period; therefore, dose levels were reduced from 300 mg/kg bw/day to 150 mg/kg bw/day from day 14 of dosing. Prior to death, animals showed loose stools, soiled fur, pale skin, irregular respiration, and decreased locomotor activity. Histopathological examination of the dead animals revealed congestion, hemorrhage, and thrombus in various organs, and phosphotungstic acid–hematoxylin positive staining of eosinophilic material was found in the kidneys and lungs. Cause of death was considered to be circulatory disturbance, presumed to be disseminated intravascular coagulation. In the highest dose group, loose stools, pale skin, and irregular respiration were observed in survivors. Body weight and food consumption were decreased during the premating period in males and females in the highest dose group. Histopathological examination in the highest dose group showed fatty changes and centrilobular hepatocellular hypertrophy, and hemosiderin deposition in the spleen in parental males and hemorrhage and macrophage aggregation in the lung and hemosiderin deposition, and increased extramedullary hematopoiesis in the spleen in parental females. Systemic toxicity observed in this study (TG421) at 300 mg/kg bw/day was more severe than that of the 28-day repeated-dose toxicity study (TG407). Age at administration (6 weeks old vs 9 weeks old; TG407 vs TG421) may affect toxic response. The reproductive organs and fertility was not affected in rats treated with *N*-ethyl-1-aminonaphthalene. On PND 4, male and female pups in the highest dose group showed decreased body weight. The NOAEL of reproductive and developmental toxicity was considered to be 60 mg/kg bw/day based on the decreased body weight observed in pups.

(5) 4, 4'-Methylenebis (2, 6-di-*tert*-butylphenol) (CAS: 118-82-1)

The repeated-dose toxicity of 4, 4'-methylenebis (2, 6-di-*tert*-butylphenol) was investigated in rats according to the OECD TG 407. Male and female rats (5 or 10 animals/sex/dose) were treated with 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol at doses of 0 (vehicle: olive oil), 8, 40, 200, and 1,000 mg/kg bw/day for 28 days. Five out of the 10 animals/sex treated with 0 and 1,000 mg/kg bw/day were assigned as a recovery group.

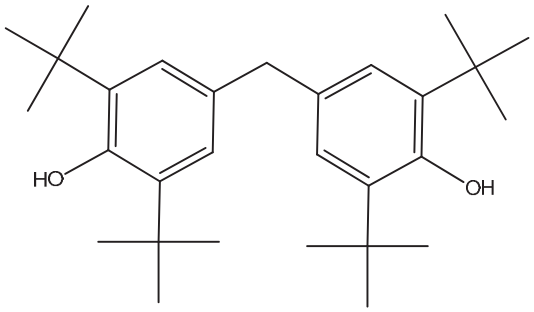

Fig. 5. Chemical structure of 4, 4'-methylenebis (2, 6-di-*tert*-butylphenol) (CAS: 118-82-1).

There were no deaths in either sex. At doses of ≥ 40 mg/kg bw/day, the relative kidney weight was increased in males, and blood cholinesterase levels were decreased in females. At doses of ≥200 mg/kg bw/day, mean corpuscular volume and mean corpuscular hemoglobin levels were decreased in males, and mean corpuscular hemoglobin concentration was decreased in females. Absolute and relative weights of the thyroid gland were increased, and histopathological analysis showed slight diffuse hyperplasia of follicular cells of the thyroid gland was increased with doses of 200 and 1000 mg/kg bw/

day. Absolute and relative weights of the ovary were increased without histopathological changes with doses of ≥200 mg/kg bw/day. These changes were no longer found after the recovery period. Based on changes in relative kidney weight and blood cholinesterase levels, the NOAEL for repeated-dose toxicity of 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol) was determined to be 8 mg/kg bw/day in rats.

A bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537, and *E. coli* WP2*uvrA* (OECD TG 471) showed negative results for 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol), with and without metabolic activation. An *in vitro* chromosome aberration test that used CHL/IU cells (OECD TG 473) showed that 4, 4'-methylenebis (2, 6-di-*tert*-butylphenol) was also negative, with and without metabolic activation. These results indicate that 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol) is nongenotoxic *in vitro*.

A reproduction/developmental toxicity screening test (OECD TG 421) was conducted to clarify the effects of 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol) on reproductive and developmental toxicity. Male rats were treated with 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol) at doses of at 0 [vehicle: 0.5% (w/v) methylcellulose solution], 100, 300, and 1,000 mg/kg bw/day for 14 days prior to mating and throughout the mating period until the day before necropsy (42 days), and female rats were treated for 14 days prior to mating and throughout the mating and gestation periods until day 4 of lactation (41–50 days). There were no mortalities with any dose during the treatment period. There were no effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity up to the highest dose. The NOAEL of 4, 4'-methylenebis(2, 6-di-*tert*-butylphenol) for reproductive and developmental toxicity was determined to be 1,000 mg/kg/day (the highest dose tested).

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