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

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Toxicological information regarding chemical substances has been collected by the Japanese Ministry of Health, Labor and Welfare according to the Japanese Chemical Substances Control Law. We have reviewed numerous toxicological studies and have created annual versions of the International Uniform Chemical Information Database（IUCLID）dossier. In FY2024, we created IUCLID dossiers for the following five chemical substances: 2,6-naphthalenedicarboxylic acid（CAS No.: 1141-38-4）, glutaric acid, dimethyl ester（CAS No.: 1119-40-0）, crotonic acid（CAS No.: 107-93-7）, cyanochlorobenzene（CAS No.: 623-03-0）, and 4-*tert*-butylcyclohexan-1-yl acetate（CAS No.: 32210-23-4）. So far, we have sought to disseminate toxicological information via IUCLID dossier using the Japan Existing Chemical Database（JECDB）. The IUCLID dossier of these five substances will be released in FY2026. This paper provides a summary of the toxicological information for these five chemical substances.

Keywords: IUCLID, existing chemical substance, toxicological assessment, JECDB

Introduction

The IUCLID[1, 2] is a database management software application that is used to record, store, maintain, and exchange data regarding intrinsic and hazardous properties of chemical substances. It was originally developed by the European Chemicals Agency in collaboration with the Organization for Economic Cooperation and Development（OECD）[1, 3]. At present, IUCLID plays a crucial role in a variety of regulatory contexts, including the EU's Registration, Evaluation, Authorization, and Restriction of Chemicals regulation[2, 4]. This platform provides a standardized framework for recording and exchanging chemical data, thereby ensuring consistency and comparability across different datasets. Moreover, data submission and review processes are streamlined by using a common format, which reduces the time and effort required for regulatory assessment. In addition, the IUCLID dossier format can be customized to fit a variety of specific regulatory contexts and needs, thereby facilitating flexible data management.

In this 11th report, we have assessed the toxicological studies related to human health risk that has been collected by the Japanese Ministry of Health, Labor and Welfare（MHLW）under the Chemical Substance Control Law of Japan. The assessment reports submitted by Japanese government, including the IUCLID dossiers for OECD Screening Information Data Sets Initial Assessment Programme and the Cooperative Chemicals Assessment Programme are available in the OECD's Existing Chemicals Database[5]. IUCLID dossiers for the toxicological studies, not submitted to the OECD by the Japanese MHLW, are published annually in the Japan Existing Chemical Database（JECDB）and can be freely used, both domestically and internationally[6]. At present, 45 IUCLID dossiers and their export files that are IUCLID software-compatible version of those dossiers are available in the JECDB, and a variety of summary reports have also been published[7–16].

In this 11th report, we summarize toxicological

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studies for the following five substances, for which we have created IUCLID dossiers that will be released in 2026: 2,6-naphthalenedicarboxylic acid (CAS No.: 1141-38-4), glutaric acid, dimethyl ester (CAS No.: 1119-40-0), crotonic acid (CAS No.: 107-93-7), cyanochlorobenzene (CAS No.: 623-03-0), and 4-*tert*-butylcyclohexan-1-yl acetate (CAS No.: 32210-23-4). Each study has been conducted in accordance with the protocols described by the Good Laboratory Practice Standards and in accordance with or similar to the OECD Guidelines for the Testing of Chemicals; combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), bacterial reverse mutation test (OECD TG 471), or *in vitro* mammalian chromosomal aberration test (OECD TG 473). In this paper, we provided a limited summary of results and highlighted those findings that were judged to be adverse effects of test substances. However, the complete hazard assessments for these chemicals were well described within the IUCLID dossiers. Ultimately, we believe that the dissemination of this toxicological information can improve global chemical safety assessment activities.

(1) 2,6-Naphthalenedicarboxylic acid (CAS No.:1141-38-4)

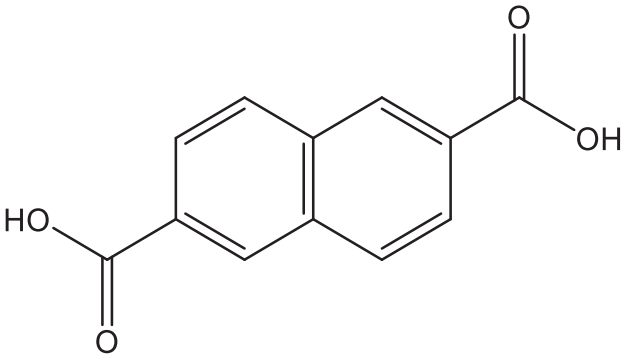

Fig. 1. Structure of 2,6-Naphthalenedicarboxylic acid (CAS No.:1141-38-4)

Repeated-dose toxicity

A combined repeated-dose toxicity study using a rat model with a reproduction and developmental toxicity screening test of 2,6-naphthalenedicarboxylic acid. Here, all experimental procedures followed prevailing Japanese guidelines (Methods of Testing New Chemicals, March 31, 2011[17]; similar to OECD TG 422). Briefly, male and female rats (12 animals/sex/dose) were given 2,6-naphthalenedicarboxylic acid via oral gavage at a dose of 0 (vehicle: 1% methyl cellulose solution), 100, 300, or 1,000 mg/kg body weight (bw)/day. Males were treated for 28 days, including a 14-day premating period and a subsequent mating period, while females were treated for 39-43 days, including 14-day premating, mating, and gestation periods until lactation day 4. Five males from 0 and 1,000 mg/kg bw/day treated group were allocated to a recovery group and were maintained for 14 days after chemical administration period of 28 days. Ten additional females were treated with 0 and 1,000 mg/kg bw/day as a satellite group. These satellite females were treated for 28 days without mating, and five females at 0 and 1,000 mg/kg bw/day were also assigned to a recovery group and maintained for 14 days after administration period.

No treatment-related deaths were noted in either sex. In mating females receiving 1,000 mg/kg bw/day, it was observed restrained body weight gain during the gestation period. In satellite females receiving 1,000 mg/kg bw/day, it was observed a decrease in red blood cell count (RBC), an increase in mean corpuscular volume (MCV), an increase in mean corpuscular hemoglobin (MCH), and an increase in the relative weight of the liver. Since these changes disappeared by the end of the recovery period, they were thought to be reversible. Based on these results, in which effects were observed only in mating and satellite females given 1,000 mg/kg bw/day, we concluded that no observed adverse effect levels (NOAELs) for repeated-dose toxicity are 1,000 mg/kg bw/day (the highest dose tested) for males and 300 mg/kg bw/day for females.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study and reproductive/developmental toxicity screening test described above, no adverse effects were observed up to the highest dose tested. The NOAEL for the reproductive and developmental toxicity was determined to be 1,000 mg/kg bw/day, which was the highest dose tested.

Genotoxicity

A bacterial reverse mutation assay using *Salmonella*

typhimurium（*S. typhimurium*）TA100, TA1535, TA98, and TA1537 with *Escherichia coli*（*E. coli*）WP2*uvr* was conducted in accordance with the Japanese guidelines（Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 471）stated above. In general, 2,6-naphthalenedicarboxylic acid showed negative results with or without rat S9 metabolic activation. Next, an *in vitro* chromosomal aberration test using Chinese hamster lung（CHL/IU）cells performed according to the Japanese guideline（Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 473）revealed that 2,6-naphthalenedicarboxylic acid was also negative, both with and without rat S9 metabolic activation. Thus, 2,6-naphthalenedicarboxylic acid was determined to be nongenotoxic *in vitro*.

（2） Glutaric acid, dimethyl ester（CAS No.:1119-40-0）

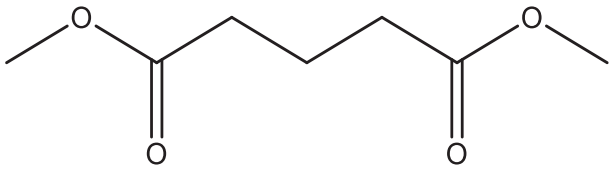

Fig. 2 . Structure of Glutaric acid, dimethyl ester（CAS No.:1119-40-0）

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test of glutaric acid, dimethyl ester, again using a rat model system. Once again, all procedures followed the Japanese guidelines（Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 422）. In brief, both male and female rats（12 animals/sex/dose）were treated with glutaric acid, dimethyl ester via oral gavage at concentrations of 0（vehicle: corn oil）, 100, 300, and 1,000 mg/kg bw/day. Males were treated for 42 days, including a 14-day premating period and a subsequent mating period, while females were treated for 41-55 days, including 14-day premating, mating, and gestation periods until lactation day 4. Five males from 0 and 1,000 mg/kg bw/day treated group were allocated to a recovery group and were maintained for 14 days after the chemical administration period for 42 days. Ten additional females were treated with 0 and 1,000 mg/kg bw/day as a satellite group. These satellite females were treated with glutaric acid, dimethyl ester for 42 days without mating, and five females at 0 and 1,000 mg/kg bw/day were assigned as a recovery group and maintained for 14 days after administration period.

One mating female in the 1,000 mg/kg bw/day group died on day 23 of gestation. It was considered that this event occurred due to changes induced by deterioration of the animal's pregnant condition and stress that was not related to the administration of glutaric acid, dimethyl ester. However, we did not have sufficient evidence to conclude that this was an accidental death.

Next, the histopathological examination of survivors revealed that hyperplasia of squamous cells within the limiting ridge of the stomach was present in males and satellite females treated at 1,000 mg/kg bw/day, indicating that mucosal irritation was induced by the test substance. However, this change disappeared in males and was reduced in satellite females by the end of the recovery period. Based on observed stomach effects in subjects receiving 1,000 mg/kg bw/day, the NOAEL for repeated-dose toxicity was determined to be 300 mg/kg bw/day for both males and females.

Reproductive and developmental toxicity

In the screening test described above, it was observed no adverse effects on reproductive and developmental parameters up to the highest dose tested. The NOAEL for the reproductive and developmental toxicity was determined to be 1,000 mg/kg bw/day（i.e., the highest dose tested）.

Genotoxicity

A bacterial reverse mutation assay with *S. typhimurium* TA100, TA1535, TA98, TA1537 and *E. coli* WP2*uvrA* was used to determine *in vitro* mutagenicity. This assay was conducted in accordance with OECD TG 471 and the above stated Japanese guidelines. Overall, glutaric acid, dimethyl ester treatment was not mutagenic, either with or without rat S9 metabolic activation. An *in vitro* chromosomal aberration test using CHL/IU cells was performed according to the OECD TG 473 and Japanese guidelines stated above. This also indicated that glutaric acid, dimethyl ester was negative with or without rat S9 metabolic activation. Consequently,

glutaric acid, dimethyl ester was determined to be nongenotoxic *in vitro*.

(3) Crotonic acid (CAS No.:107-93-7)

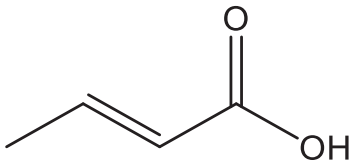

Fig. 3. Structure of Crotonic acid (CAS No.:107-93-7)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test for crotonic acid using the same rat model. This screening was performed according to existing Japanese guidelines (Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 422). Specifically, male and female rats (12 animals/sex/dose) were treated with crotonic acid via oral gavage at doses of 0 (vehicle: corn oil), 50, 150, and 500 mg/kg bw/day. Males were dosed for 42 days, including a 14-day premating period and a subsequent mating period. Females were dosed for 41-48 days, including 14-day premating, mating, and gestation periods until lactation day 4. Of the 12 males treated with 0 and 500 mg/kg bw/day doses, five were assigned as a recovery group then maintained for 14 days after the administration period. Ten additional females were treated with 0 and 500 mg/kg bw/day as a satellite group. These satellite females were treated 42 days without mating, and five females at 0 and 1,000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after administration period.

No treatment-related deaths were noted in either sex. It was observed reduced body weight gain in males and mating females receiving 500 mg/kg bw/day. Moreover, suppression of body weight gain observed in mating females during gestation and lactation periods was accompanied by a decrease in food consumption. Hematological analysis revealed increases in RBC and platelet count, decreases in MCH and mean corpuscular hemoglobin concentration in satellite females receiving 500 mg/kg bw/day. Blood clinical chemistry analysis showed decreases in total protein and albumin in males receiving 500 mg/kg bw/day as well as a decrease in total cholesterol in satellite females receiving 500 mg/kg bw/day. Thickening of the forestomach wall was identified in both males and mating females receiving 500 mg/kg bw/day, and gross autopsy results also found a raised focus in the forestomach of mating females receiving 500 mg/kg bw/day. Histopathological examination revealed hyperplasia of squamous cells in the forestomach in mating and satellite females receiving 500 mg/kg bw/day as well as in males receiving ≥ 150 mg/kg bw/day. However, these changes were reduced or no longer observed by the end of the recovery period. Since crotonic acid is a known skin irritant, the changes observed here were thought to be caused by direct irritating effects related to oral administration. Overall, on the basis of observed decreases in body weight gain and the appearance of forestomach lesions, the NOAELs for repeated-dose toxicity were determined to be 50 mg/kg bw/day for males and 150 mg/kg bw/day for females.

Reproductive and developmental toxicity

In the screening test described above, no adverse effects on reproductive and developmental parameters were detected even at the highest doses tested. Therefore, the NOAEL for reproductive and developmental toxicity was determined to be 500 mg/kg bw/day (i.e., the highest dose tested).

(4) Cyanochlorobenzene (CAS No.:623-03-0)

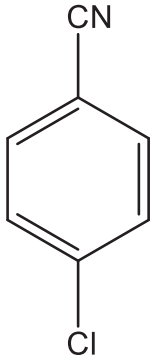

Fig. 4. Structure of Cyanochlorobenzene (CAS No.:623-03-0)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test of cyanochlorobenzene was performed using the rat model system described above. All experiments were

performed according to Japanese guidelines (Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 422). Briefly, male and female rats (12 animals/sex/dose) were treated with cyanochlorobenzene via oral gavage at doses of 0 (vehicle: 1%, methyl cellulose), 3, 10, and 30 mg/kg bw/day. Males were dosed for 28 days, including a 14-day premating period and a subsequent mating period. In contrast, females were dosed for 39-51 days, including 14-day premating, mating, and gestation periods, with the experiment continuing until lactation day 4. Of the 12 males treated with 0 and 30 mg/kg bw/day doses, five were assigned as a recovery group and subsequently maintained for 14 days after the administration period. Ten additional females were treated with 0 and 30 mg/kg bw/day as a satellite group. These satellite females were treated for 42 days without mating, and five females at 0 and 30 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after administration period.

No deaths were observed in either sex. Food consumption decreased in both sexes treated with 30 mg/kg bw/day and increases in total cholesterol (T-Cho) and triglycerides were observed in both males and satellite females receiving 30 mg/kg bw/day. However, these changes were not observed after the recovery period. Relative liver weights were increased in males and mating females and mean absolute and relative liver weights also increased in satellite females at 30 mg/kg bw/day. No corresponding abnormal findings were observed on histopathological examination. However, increases in T-Cho and triglycerides suggest that the test substance may have exerted an effect on the liver. Overall, the relative liver weight of the satellite females remained high by the end of the recovery period; however, this value was lower than that at the end of the treatment period, suggesting that this effect may be reversible. It was observed increases in the relative kidney weight of males receiving ≥10 mg/kg bw/day and the absolute kidney weight of males receiving 30 mg/kg bw/day. Histopathological examination showed an eosinophilic body in the proximal tubule of the kidney. This may result from α2u-globulin accumulation in rats receiving ≥10 mg/kg bw/day. Overall, the effects of α2u-globulin accumulation on the kidney appeared to be specific to male rats and cannot be extrapolated to humans; therefore, they were not considered to be toxic effects. As a result, the NOAEL for repeated-dose toxicity was determined to be 10 mg/kg bw/day for liver weight changes at 30 mg/kg bw/day in both males and females and increase the levels of T-Cho and triglycerides in males and satellite females.

Reproductive and developmental toxicity

No effects on reproductive organ function or fertility were observed following cyanochlorobenzene treatment. Moreover, the body weights of both male and female pups were significantly lower or tended to be lower in the 10 and 30 mg/kg bw/day groups by postnataldays (PND) 0 and 4. Therefore, the NOAEL for the reproductive and developmental toxicity was determined to be 30 mg/kg bw/day for parent animals (highest dose tested) and 3 mg/kg bw/day for pups.

(5) 4-*tert*-Butylcyclohexan-1-yl acetate (CAS No.: 32210-23-4)

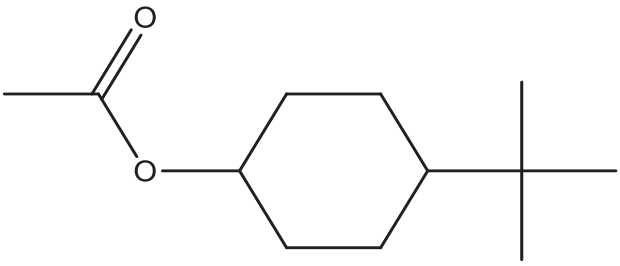

Fig. 5 . Structure of 4-*tert*-Butylcyclohexan-1-yl acetate (CAS No.: 32210-23-4)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test of 4-*tert*-butylcyclohexan-1-yl acetate was performed using the rat model system. As before, all experiments were performed according to Japanese guidelines (Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 422). First, male and female rats (12 animals/sex/dose) were treated with 4-*tert*-butylcyclohexan-1-yl acetate via oral gavage at doses of 0 (vehicle: corn oil), 30, 100, or 300 mg/kg bw/day. Males were dosed for 42 days, including a 14-day premating period and a subsequent mating period, while females were dosed for 42-51 days depending on timing of pregnancy, including 14-day premating, mating, and gestation periods. The experiment lasted

until day 4 of lactation. Of the 12 males treated with 0 and 300 mg/kg bw/day, five were assigned to a recovery group and maintained for 14 days after the administration period. Ten additional females were treated with 0 and 300 mg/kg bw/day as a satellite group. These satellite females were treated for 42 days without mating, and five females at 0 and 300 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

No treatment-related deaths were noted in either sex. However, decreased spontaneous movement, salivation, and convulsions were observed in both sexes in the 300 mg/kg bw/day group throughout the treatment period. When observed more closely, convulsions were found in mating females receiving 300 mg/kg bw/day and a flattened posture and a decrease in rearing was found in satellite females receiving 300 mg/kg bw/day. Suppression of body weight gain accompanied by decreased food consumption was observed in mating females receiving 300 mg/kg bw/day during premating period, and low body weight was also observed in mating females during the gestation period. The hematological examination revealed decrease in RBC and increases in MCV and MCH in the satellite females receiving 300 mg/kg bw/day.

It was found that the relative weight of the liver was higher in both sexes treated with 300 mg/kg bw/day than 0 mg/kg bw/day, while the relative weight of adrenal gland was higher in mating females receiving 300 mg/kg bw/day than 0 mg/kg bw/day. The relative weight of the kidney was increased in mating females at 300 mg/kg bw/day, while the absolute and relative kidney weights were increased in males receiving doses ≥100 mg/kg bw/day. Further histopathological examination of male kidney samples showed eosinophilic bodies in tubular epithelial cells in male rats receiving ≥30 mg/kg bw/day, enhanced tubule regeneration in male rats receiving ≥100 mg/kg bw/day, and granular casts in male rats receiving 300 mg/kg bw/day. Moreover, the eosinophilic bodies in the tubular epithelial cells observed in males receiving ≥30 mg/kg bw/day were positive for anti-α2u-globulin immunohistochemical staining. These findings are not relevant for humans as mentioned above. Hypertrophy of centrilobular hepatocytes was observed in mating and satellite females receiving 300 mg/kg bw/day as well as increased vacuoles in the zona fasciculata of the adrenal gland in both satellite females receiving 300 mg/kg bw/day and mating females receiving ≥100 mg/kg bw/day. All of these changes, except for the regenerated renal tubule, were no longer observed after the recovery period, showing that they were reversible. Based on these results, the NOAEL for repeated-dose toxicity was determined to be 30 mg/kg bw/day for increased absolute and relative kidney weights, for increased enhanced regeneration of tubules in males, and for increased vacuole size in the zona fasciculata of the adrenal gland in mating females.

Reproductive and developmental toxicity

Treatment-related decreases in nursing behavior were observed in one dam from each in the 100 and 300 mg/kg bw/day groups. Moreover, this began on day 1 of lactation, and all pups of those dams died before lactation day 4. Next, in the dam receiving 100 mg/kg bw/day, histopathological examination showed decreased lactation of the mammary gland and a smaller corpus luteum in the ovary. In the dam receiving 300 mg/kg bw/day, a fracture of the incisor was found on day 2-4 of lactation, and gross pathological analysis revealed that the mammary gland was found to be undeveloped at the inguinal. Further histopathological analyses revealed decreased lactation in the mammary gland, atrophy of goblet cells in the colon, vacuolation of renal tubular epithelial cells, dilatation and necrosis of renal tubules, decreased granules of granular ducts in the submandibular gland, thymic atrophy, and aggregation of alveolar macrophages. Taken together, these changes may be related to decreased nursing behavior or to a deterioration in condition due to poor feeding associated with incisor fracture. A tendency of a lower viability index by PND 4 in treatment groups was observed. Therefore, the NOAEL for reproductive and developmental toxicity was determined to be 300 mg/kg bw/day for males and 30 mg/kg bw/day for dams and pups.

Genotoxicity

A bacterial reverse mutation assay involving *S. typhimurium* TA100, TA1535, TA98, and TA1537, as well as *E. coli* WP2*uvrA* were conducted in accordance

with OECD TG 471 and the Japanese guidelines stated above. Overall, 4-*tert*-butylcyclohexan-1-yl acetate showed negative results with or without rat S9 metabolic activation. A further *in vitro* chromosomal aberration test using CHL/IU cells performed according to OECD TG 473 and Japanese guidelines revealed that 4-*tert*-butylcyclohexan-1-yl acetate also scored negative, regardless of whether samples experienced rat S9 metabolic activation. Thus, 4-*tert*-butylcyclohexan-1-yl acetate was determined to be nongenotoxic *in vitro*.

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