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

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Under the Japanese Chemical Substances Control Law（CSCL）, toxicological information for existing chemical substances has been collected by the Japanese Ministry of Health, Labor, and Welfare. We have taken the initiative to disseminate information via the Japan Existing Chemical Database（JECDB）. We have reviewed the toxicological studies and presented a summary of our evaluation of the following five substances: polyoxyethylene sorbitan fatty acid（C12-18）ester（CAS: 9005-70-3）, octylic acid（CAS: 124-07-2）, 1,3-propanediol, 2-butyl-2-ethyl（CAS: 115-84-4）, 2,4-di-tert-pentylphenol（CAS: 120-95-6）, and 1,2-ethanediyl ester octadecanoic acid（CAS: 627-83-8）. The International Uniform Chemical Information Database（IUCLID）dossiers created for these five chemical substances are available at the JECDB.

Keywords: existing chemical substance, toxicological assessment, JECDB

Introduction

The Japanese Chemical Substances Control Law（CSCL）was settled to prevent the chemical pollution in 1973[1]. It was at the start of CSCL that environmental pollution by polychlorinated biphenyl caused a serious health hazard in the Kitakyushu area.

The purpose of this law is to prevent the pollution by chemical substances that have the risk of abusing human health and disrupting the ecology and ecosystem. The examination before putting the chemicals on the market and the administration after launch of the target chemicals have been continuously conducted, with a focus on the degradable, accumulation, chronic toxicity, and flora and fauna toxicity. The newly applied chemicals are investigated and screened to figure out the priority of the risk assessment, just as the existing chemical substances are assessed and regulated.

Meanwhile, the existing chemical substances marketed before 1973 are also investigated for the screening, and the Ames test, the *in vitro* chromosomal aberration test, and the combined repeated-dose toxicity study with the reproduction or developmental toxicity screening test, etc., are conducted by the Japanese government to gather necessary toxicological information. The results of the toxicological tests for the existing chemical substances and the formatted test outline as the International Uniform Chemical Information Database（IUCLID）have been unified and managed by the National Institute of Health Sciences（NIHS）[2]. These were loaded into the Japan Existing Chemical Database（JECDB）and shared both inside and outside Japan[3].

Summaries of hazard assessments were reported annually[4-10]. This year, in this eighth report, we present summary hazard information for the following five chemical substances: (1) polyoxyethylene sorbitan fatty acid（C12-18）ester（CAS: 9005-70-3）, (2) octylic acid（CAS: 124-07-2）, (3) 1,3-propanediol, 2-butyl-2-ethyl（CAS: 115-84-4）, (4) 2,4-di-tert-pentylphenol（CAS: 120-95-6）, and (5) 1,2-ethanediyl ester octadecanoic acid（CAS: 627-83-8）.

No toxicological studies on these chemical substances have been reported previously. We consider this task

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to be of vital importance, as the public needs to receive a wider dissemination of such information. One of the most pressing challenges worldwide at present in the field of risk assessment of chemical substances is avoiding the duplication of assessment work performed by other programs or countries.

Sharing the information would help to prevent unnecessary animal studies. It also provides global access to meaningful toxicity information.

(1) Polyoxyethylene sorbitan fatty acid (C12-18) ester (CAS: 9005-70-3)

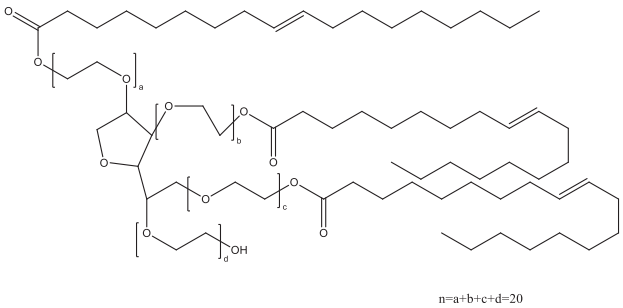

Fig. 1. Structure of polyoxyethylene sorbitan fatty acid (C12-18) ester (CAS: 9005-70-3)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with OECD TG 422 (adapted in 1996). Male and female rats (12 animals/sex/dose) were administered polyoxyethylene sorbitan fatty acid (C12-18) ester by gavage at 0 (vehicle: water for injection), 62.5, 250, and 1,000 mg/kg bodyweight/day. Males were dosed for 28 days, including a 14-day premating period and a subsequent 14-day period. Females were dosed for 42–54 days, including a 14-day premating, mating, and gestation period, and until day 4 of lactation. Six males from each group were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females were treated at 0 and 1,000 mg/kg bodyweight/day, and five additional females were treated at 62.5 and 250 mg/kg bodyweight/day as a satellite group. These females were dosed with test substance for 28 days without mating, and five were treated at 0 and 1,000 mg/kg bodyweight/day, allocated to a recovery group, and maintained for 14 days after the administration period. No deaths were recorded, and there were no changes in clinical signs, detailed clinical signs (functional observational battery: FOB), grip strength, motor activity, bodyweight, food consumption, water consumption, urinalysis, clinical biochemistry, gross pathology, or histopathology in any of the dose groups for both males and females at the end of the administration and recovery periods. The following findings were observed in the examination at the end of the administration period: In terms of hematology, decreases in hematocrit and hemoglobin were observed in females at 1,000 mg/kg bodyweight/day. In the organ weight, a significant increase in absolute and relative liver weights and a significant increase in absolute adrenal weight were observed in females at 1,000 mg/kg bodyweight/day. A tendency for an increase in relative adrenal weight was observed in females at 1,000 mg/kg bodyweight/day. However, these organ weight changes were considered minor and insignificant in toxicity assessment because there was no abnormality in histopathological examination and the increase was substantially small compared to historical control data. By contrast, there was no adverse effect related to polyoxyethylene sorbitan fatty acid (C12-18) ester in males. Based on these results, the no observed adverse effect level (NOAEL) for repeated-dose toxicity was considered to be 1,000 mg/kg bodyweight/day in males and 250 mg/kg bodyweight/day in females.

Genotoxicity

In a bacterial reverse mutation assay with *Salmonella typhimurium* (*S. typhimurium*) TA100, TA98, TA1535, and TA1537 and *Escherichia coli* (*E. coli*) WP2 *uvrA* (OECD TG 471), polyoxyethylene sorbitan fatty acid (C12-18) ester was negative with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster (CHL/IU) cells (OECD TG 473), polyoxyethylene sorbitan fatty acid (C12-18) ester was also negative with and without metabolic activation. Based on these results, polyoxyethylene sorbitan fatty acid (C12-18) ester was considered non-genotoxic *in vitro*.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test (OECD TG 422) described above, a significant decrease or a decreasing trend of bodyweight in male and female pups at 1,000 mg/kg bodyweight/day was

observed on lactation day 0.

In parental animals, there were no changes in the number of estrous cases, pairs with successful copulation, conceiving days, copulation index, fertility index, length of gestation, corpora lutea, gestation index, delivery condition, or nursing condition. In offspring animals, there were no changes in pups born, stillbirths, live pups born, the sex ratio at birth, delivery index, birth index, live birth index, live pups on day 4 of lactation, sex ratio on day 4 of lactation viability index, and general clinical signs, and there were no external abnormalities. There were no abnormalities in gross necropsy findings in stillbirths and live or dead pups, whereas the following finding was observed in the examination at the end of the administration period. The bodyweight of pups born was significantly decreased in males and tended to be decreased in females at 1,000 mg/kg bodyweight/day. Based on these results, the NOAEL for the reproduction/developmental toxicity was determined to be 250 mg/kg bodyweight/day.

(2) Octylic acid (CAS: 124-07-2)

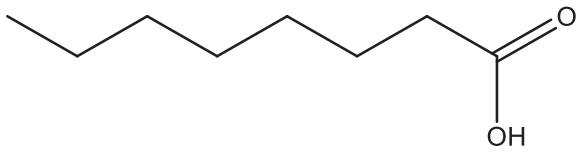

Fig. 2. Structure of octylic acid (CAS: 124-07-2)

Repeated-dose toxicity

A combined repeated-dose study with a reproductive and developmental toxicity screening test was performed in accordance with OECD TG 422 (adapted in 1996). Male and female rats (12 animals/sex/dose) were administered octylic acid by gavage at 0 (vehicle: 0.5% methylcellulose), 62.5, 250, and 1,000 mg/kg bodyweight/day. Males were dosed for 28 days, including a 14-day premating period and a subsequent 14-day period. Females were dosed for 42–46 days, including a 14-day premating, mating, and gestation period, and until day 4 of lactation. Six males from each group were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females were treated at 0 and 1,000 mg/kg bodyweight/day, and five additional females were treated with 62.5 and 250 mg/kg bodyweight/day as a satellite group. These females were dosed with the test substance without mating for 28 days, and five were treated at 0 and 1,000 mg/kg bodyweight/day, assigned to a recovery group, and kept for 14 days after the administration period.

No deaths were recorded, and there were no changes in clinical signs, detailed clinical signs (FOB), grip strength, motor activity, bodyweight, food consumption, water consumption, urinalysis, hematology, or organ weight in any of the dose groups for both males and females at the end of the administration and recovery periods. In the clinical biochemistry, a significant decrease in blood urea nitrogen and an increase in inorganic phosphorus in males at 1,000 mg/kg bodyweight/day and an increase in potassium in non-mating females at 1,000 mg/kg bodyweight/day at the end of the administration period were observed. In gross pathology, thickening of the forestomach was observed in males and non-mating females at 250 mg/kg bodyweight/day and above and in mating females at 1,000 mg/kg bodyweight/day at the end of the administration period. In the histopathological examination, squamous epithelium hyperplasia of the forestomach was observed in males and non-mating females at 62.5 mg/kg bodyweight/day and above, and in mating females at 1,000 mg/kg bodyweight/day at the end of the administration period. Also, ulceration of the forestomach was observed in males and non-mating females at 250 mg/kg bodyweight/day and in mating females at 1,000 mg/kg bodyweight/day at the end of the administration period. In addition, at the end of the recovery period, the squamous epithelium hyperplasia of the forestomach was observed in males at 250 mg/kg bodyweight/day and above and in non-mating females at 1,000 mg/kg bodyweight/day. Based on these effects, the lowest observed adverse effect level (LOAEL) for repeated-dose toxicity was considered to be 62.5 mg/kg bodyweight/day.

Genotoxicity

In a bacterial reverse mutation assay with *S. typhimurium* TA100, TA98, TA1535, and TA1537 and *E. coli* WP2 *uvrA* (OECD TG 471), octylic acid was as negative with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster (CHL/IU) cells (OECD TG 473), octylic acid was also negative with and without metabolic activation. Based on these results, octylic acid was

considered non-genotoxic *in vitro*.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test (OECD TG 422) described above, no adverse effects on reproductive and developmental parameters were observed up to the highest dose tested. Based on these effects, the NOAEL for reproduction/developmental toxicity was considered to be 1,000 mg/kg bodyweight/day (the highest dose tested).

(3) 1,3-Propanediol, 2-butyl-2-ethyl (CAS: 115-84-4)

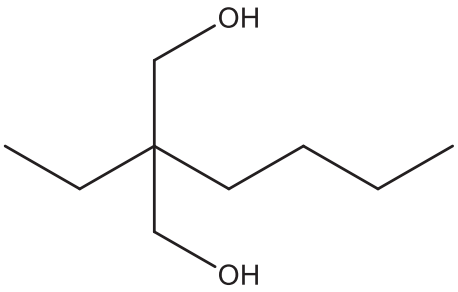

Fig. 3. Structure of 1,3-propanediol, 2-butyl-2-ethyl (CAS: 115-84-4)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with OECD TG 422 (adapted in 1996). Male and female rats (12 animals/sex/dose) were administered 1,3-propanediol, 2-butyl-2-ethyl by gavage at 0 (vehicle: 0.5% methyl cellulose), 20, 100, and 500 mg/kg bodyweight/day. Males were dosed for 42 days, which included a 14-day premating period, a 14-day mating period, and a subsequent 14-day period. Females were dosed for 41–46 days, which included a 14-day premating, mating, and gestation period and until day 4 of lactation. Five males at the 0 and 500 mg/kg bodyweight/day doses were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females at the 0 and 500 mg/kg bodyweight/day doses were treated as a satellite group. These females were dosed with test substances for 42 days without mating, and five females from each group were allocated to a recovery group and maintained for 14 days after the administration period.

No deaths were observed in either sex. The following findings were observed during or at the end of the administration period: In terms of the clinical signs, ataxia was observed in males and females at 500 mg/kg bodyweight/day, and prone or lateral position was observed in mating females at 500 mg/kg bodyweight/day. In the locomotor activity measurement, a decrease in locomotor activity was observed in mating females at 500 mg/kg bodyweight/day. In the urinalysis, a decreasing tendency in urine pH was observed in males and non-mating females at 500 mg/kg bodyweight/day. In the organ weights, an increase in relative liver weight was observed in males and females at 500 mg/kg bodyweight/day. An increase in relative kidney weight was observed in males at 100 mg/kg bodyweight/day. Increases in absolute and relative kidney weights were observed in males at 500 mg/kg bodyweight/day. In the gross pathology, thickening in the limiting ridge of the stomach was observed in males at 500 mg/kg bodyweight/day. In the histopathological examination, granular cast, tubular regeneration, and eosinophilic body in the tubular epithelial cell of kidney were observed in males at 100 mg/kg bodyweight/day and above, and tubular dilatation, necrosis, or desquamation in the tubular epithelial cell of the kidney were observed in males at 500 mg/kg bodyweight/day. We have treated changes in the kidney of male rats as adverse effects because immunostaining was not conducted to confirm for α2u-globulin in this study. Hyperplasia of squamous cells in the limiting ridge of the stomach was observed in males and non-mating females at 500 mg/kg bodyweight/day. These effects were mitigated by a recovery period of 14 days. Based on these effects, the NOAEL for repeated-dose toxicity was 20 mg/kg bodyweight/day in males and 100 mg/kg bodyweight/day in females.

Genotoxicity

In a bacterial reverse mutation assay with *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA*/ PKM101 (OECD TG 471), 1,3-propanediol, 2-butyl-2-ethyl was negative with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster (CHL/IU) cells (OECD TG 473), 1,3-propanediol, 2-butyl-2-ethyl was also negative with and without metabolic activation. Based on these results, 1,3-propanediol, 2-butyl-2-ethyl was considered non-genotoxic *in vitro*.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study with the reproduction and developmental toxicity screening test described above. No treatment-related effects were observed on reproduction or developmental parameters. The NOAEL for reproduction and developmental toxicity was 500 mg/kg bodyweight/day (the highest dose tested).

(4) 2,4-Di-*tert*-pentylphenol (CAS: 120-95-6)

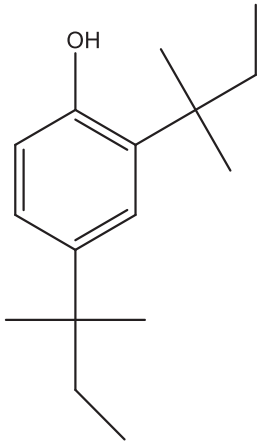

Fig. 4. Structure of 2,4-di-*tert*-pentylphenol (CAS: 120-95-6)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with OECD TG 422 (adapted in 1996). Male and female rats (13 animals/sex/dose) were administered 2,4-di-*tert*-pentylphenol by gavage at 0 (vehicle: corn oil), 10, 50, and 100 mg/kg bodyweight/day for 42 days. Initially, 250 mg/kg bodyweight/day of 2,4-di-*tert*-pentylphenol was administered as the highest dose; however, the highest concentration was changed to 100 mg/kg bodyweight/day after the 12th day of administration, because more than half of the test individuals were dying or dead.

To investigate the recovery property of male rats, five individuals of 0 and 50 mg/kg bodyweight/day were kept for an additional 14 days until necropsy without administration. Females at 0, 10 and 50 mg/kg bodyweight/day were dosed for 41–44 days, including a 14-day premating, mating, and gestation period until day 4 of lactation. Ten additional females were treated at doses of 0 and 100 mg/kg bodyweight/day, and five additional females were treated as a satellite group. These females were dosed with 2,4-di-*tert*-pentylphenol for 42 days without mating, and five of the females at 0 and 100 mg/kg bodyweight/day were allocated to a recovery group and maintained for 14 days after the administration period.

Death or moribund sacrifice occurred in 9 of 13 high-dose males on days 6–13 and in 8 of 13 high-dose mating females and 4 of 10 females in satellite group on days 6–9. These animals showed changes in clinical signs from day 2 of administration. In the kidneys of dead or sacrificed animals, extensive degeneration and necrosis were observed in the cortical and medullary tubules, neutrophil infiltration in the renal papillary interstitium, and hyperplasia of the transitional epithelium of the renal pelvis. Changes in clinical signs during the administration period in survivors included transient salivation at ≥50 mg/kg bodyweight/day in males, at 100 mg/kg bodyweight/day in non-mating females, and at 50 mg/kg bodyweight/day in delivered females. Loose stools were observed in males and non-mating females at 100 mg/kg bodyweight/day. In terms of motor activity, a decrease in locomotor activity was observed in non-mating females at 100 mg/kg bodyweight/day. The bodyweight and food consumption of males who were administered 100 mg/kg were lower than those of the control group and were also significantly lower in satellite females administered 100 mg/kg. In the urinalysis, urine volume was increased in non-mating females by 100 mg/kg bodyweight/day. Regarding other symptoms and function, there were no treatment-related effects observed in both males and females.

In hematology, decreases in hemoglobin and hematocrit and a trend toward a decrease in red blood cell count were observed in males at 100 mg/kg bodyweight/day. Additionally, prolonged prothrombin time and an extension tendency of thromboplastin time were observed. In non-mating females at 100 mg/kg bodyweight/day, decreases in red blood cell count, hemoglobin, and hematocrit were observed.

At 50 mg/kg bodyweight/day, there was a drop in mean corpuscular hemoglobin concentration and a rise in the reticulocyte ratio in delivered females. At 100 mg/kg bodyweight/day, alkaline phosphatase activity in males tended to rise in blood biochemistry. In organ weight, at the end of the administration period, increased absolute and/or relative weights

of the liver were observed in males at 50 mg/kg bodyweight/day and higher, non-mating females at 100 mg/kg bodyweight/day, and delivered females at 50 mg/kg bodyweight/day. Increased relative spleen weights were observed in non-mating females at 100 mg/kg bodyweight/day. Increased absolute and relative spleen weight was also observed in non-mating females at 100 mg/kg bodyweight/day at the end of the recovery period.

In the histopathology, basophilic tubules and casts were observed in the cortex and medulla of the kidneys of males at 100 mg/kg bodyweight/day. Basophilic tubules were observed in the renal cortex at 100 mg/kg bodyweight/day in non-mating females.

In addition, signs or symptoms at the end of administration were recovered or mitigated after the recovery period. Based on these effects, the NOAEL was considered to be 10 mg/kg bodyweight/day for repeated-dose oral toxicity.

Genotoxicity

A bacterial reverse mutation assay with *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA* (OECD TG 471) was performed with and without metabolic activation. 2,4-Di-*tert*-pentylphenol was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test using CHL/IU cells (OECD TG 473) showed positive results by short-time high-dose (0.015 mg/mL) processing with metabolic activation. Based on these results, 2,4-di-*tert*-pentylphenol was considered to be clastogenic *in vitro*.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test (OECD TG 422) described above, though one death during the parturition and one moribund on the day of parturition were observed in 50 mg/kg bodyweight/day administered dams, no other adverse effects on reproductive parameters or development were observed up to 50 mg/kg bodyweight/day. Based on these results, the NOAEL was considered to be 50 mg/kg bodyweight/day for reproductive and developmental toxicity.

(5) 1,2-Ethanediyl ester octadecanoic acid (CAS: 627-83-8)

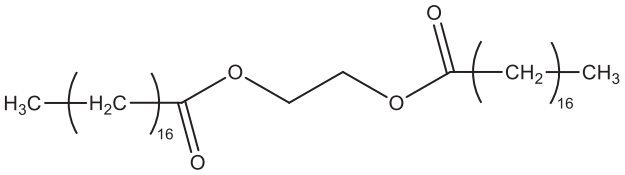

Fig. 5. Structure of 1,2-ethanediyl ester octadecanoic acid (CAS: 627-83-8)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with OECD TG 422 (adapted in 1996). Male and female rats (12 animals/sex/dose) were administered 1,2-ethanediyl ester octadecanoic acid by gavage at 0 (vehicle: 0.5 w/v% methylcellulose solution), 100, 300, and 1,000 mg/kg bodyweight/day. Males were dosed for 42 days, including a 14-day premating period and subsequent mating period, whereas females in the mating group were dosed for 41–46 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Five males at the 0 and 1,000 mg/kg bodyweight/day doses were allocated to a recovery group and maintained for 14 days after the administration period. Ten additional females were dosed at 0 and 1,000 mg/kg bodyweight/day as a satellite group. These females were dosed for 42 days without mating, and five females at 0 and 1000 mg/kg bodyweight/day were allocated to a recovery group and maintained for 14 days after the administration period.

There were no treatment-related effects on mortality, clinical signs, detailed clinical signs (FOB), grip strength, locomotor activity, bodyweight, food intake, urinalysis, hematologic findings, clinical biochemical findings, organ weight and histopathological findings at any dose. Based on these results, the NOAEL for repeated-does toxicity was considered to be 1,000 mg/kg bodyweight/day.

Genotoxicity

In a bacterial reverse mutation assay with the TA100, TA1535, TA98, and TA1537 strains of *S. typhimurium* and the WP2 *uvrA* strain of *E. coli* (OECD TG 471), 1,2-ethanediyl ester octadecanoic acid was negative both with and without metabolic

Table 1. List of evaluation values and the genotoxicity of each substance.

	Repeated-dose toxicity test		Reproductive/developmental toxicity test		Genotoxicity test	
CAS No.	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Ames test	Chromosomal aberration test
9005-70-3	male: 1,000 female: 250	male: NA female: 1,000	250	1,000	Negative	Negative
124-07-2	NA	62.5	1,000	NA	Negative	Negative
115-84-4	male: 20 female: 100	male: 100 female: 500	500	NA	Negative	Negative
120-95-6	10	50	50	100	Negative	Positive
627-83-8	1,000	NA	1,000	NA	Negative	Negative

NOAEL: No Observed Adverse Effect Level; LOAEL: Lowest Observed Adverse Effect Level
NA: Not Available

activation. In an *in vitro* chromosomal aberration test using CHL/IU cells (OECD TG 473), the results were negative with and without metabolic activation. Based on these results, 1,2-ethanediyl ester octadecanoic acid is considered to be non-genotoxic *in vitro*.

Reproductive and developmental toxicity

In the combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described above, no treatment-related effects were observed on reproduction or developmental parameters. The NOAEL for the reproduction and developmental toxicity was 1,000 mg/kg bodyweight/day (the highest dose tested).

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