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Summary of human health hazard assessment of existing chemical substances (X)

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Toxicological information on existing chemical substances has been collected by the Japanese Ministry of Health, Labour and Welfare in accordance with the Japanese Chemical Substances Control Law. Herein, we disseminate information via the Japan Existing Chemical Database (JECDB). We reviewed and summarized several toxicological examinations of the following five substances: (1) Benzyl(dimethyl)octan-1-yl)ammonium chloride (CAS No.: 959-55-7), (2) *cis*-3-hexenyl-salicylate (CAS No.: 65405-77-8), (3) undecanal (CAS No.: 112-44-7), (4) methyl 3-methoxypropanoate (CAS No.: 3852-09-3), and (5) 1-ethoxy-2-(2-methoxyethoxyethane (CAS No.: 1002-67-1). The International Uniform Chemical Information Database (IUCLID) dossiers for these five substances are available in the JECDB.

Keywords: existing chemical substance, toxicological assessment, JECDB

Introduction

Polychlorinated biphenyls (PCBs) had been recognized as causing chemical hazards for humans and the environment. In keeping with this fact, the Chemical Substance Control Law (CSCL) was established and enacted in Japan in 1973 to regulate using, producing, and importing chemical substances to prevent harm and pollution caused by them to human health and the environment. In the CSCL, chemical substances that were on the market before 1973 are designated as the existing chemical substances. The Ministry of Health, Labour and Welfare (MHLW) in Japan has collected the safety data on existing substances, including data on repeated-dose, reproductive/development toxicity, and genotoxicity. We have assessed these toxicological data[1)–9)], and our reports for the Organization for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS) Initial Assessment Programme and Cooperative Chemicals Assessment Programme (CoCAP) are available in the OECD Existing Chemicals Database[10)].

In this tenth report, we summarized toxicological studies for the following five substances: (1) Benzyl (dimethyl)(octan-1-yl)ammonium chloride (CAS No.: 959-55-7), (2) cis-3-hexenyl salicylate (CAS No.: 65405-77-8), (3) undecanal (CAS No.: 112-44-7), (4) methyl 3-methoxypropanoate (CAS No.: 3852-09-3), and (5) 1-ethoxy-2-(2-methoxyethoxy)ethane (CAS No.: 1002-67-1). Each study was conducted in accordance with Good Laboratory Practice Standards and in accordance with the OECD Guidelines for the Testing of Chemicals; for 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). The hazard assessment of these chemicals is well described in the International Uniform Chemical Information Database dossiers, which are internationally available in the Japan Existing Chemical Database (JECDB)[11)]. We provide a summary of the examination results, especially findings determined as adverse effects of the test substance. Sharing these toxicological information

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helps to provide global access to important toxicity information.

(1) Benzyl (dimethyl) (octan-1-yl) ammonium chloride (CAS No.: 959-55-7)

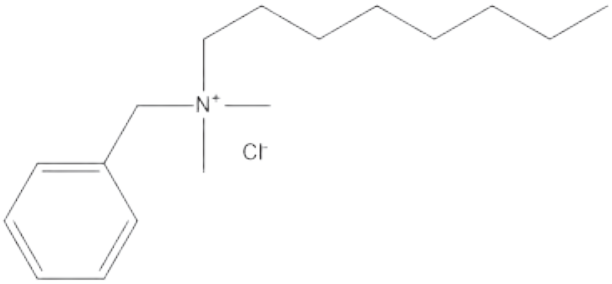

Fig. 1. Structure of benzyl (dimethyl) (octan-1-yl) ammonium chloride (CAS No.: 959-55-7)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed according to the Japanese guidelines (Methods of Testing New Chemicals, March 31, 2011; similar to OECD TG 422). Male and female rats (12 animals/sex/dose) were administered benzyl (dimethyl) (octan-1-yl) ammonium chloride by gavage at 0 (vehicle: water for injection), 15, 50, and 150 mg/kg body weight (bw)/day. Males were dosed for 42 days, including a 14-day premating period and subsequent mating period. Females in the mating group were dosed for 41-47 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Ten additional females were dosed at 0 and 150 mg/kg bw/day as a satellite group for 42 days without mating. Five males and five females were selected from each group (males or mating/satellite females). Functional, hematological, biochemistry, and histopathological examinations were conducted for the selected animals, and urological examination was conducted for males and satellite females. Another five males and satellite females at 0 and 150 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

Deaths or moribund sacrifices occurred in 3 males, 3 mating females, and 2 satellite females at 150 mg/kg bw/day. These animals exhibited gasping and a decrease in body weight or restraint of body weight gain. Histopathology of dead or moribund animals showed necrotizing inflammation in the trachea and bronchus, and alveolar edema and bronchiolo-alveolar inflammation in the lung. Therefore, benzyl (dimethyl) (octan-1-yl) ammonium chloride, which is classed as an irritant, probably entered the respiratory tract via aspiration, causing respiratory failure, deterioration of the general condition, and death.

In clinical observations, transient salivation was observed in males and mating females at 150 mg/kg bw/day and was probably due to the irritant property of benzyl (dimethyl) (octan-1-yl) ammonium chloride.

A body weight gain in males was restrained at ≥50 mg/kg bw/day. A transient but significant decrease in the food consumptions was observed on day 2 in males at ≥50 mg/kg bw/day and in mating females at 150 mg/kg bw/day.

The urinalysis showed that brown urine was observed in males and satellite females at 150 mg/kg bw/day.

The hematology analysis showed that fibrinogen decreased in males and females at 150 mg/kg bw/day.

In the biochemistry analysis, total bile acid (TBA) decreased in males and females, and furthermore, sodium and chloride decreased in mating females, at 150 mg/kg bw/day.

The gross pathological examinations found large cecum without relevant histopathological findings in males at ≥50 mg/kg bw/day and in females at 150 mg/kg bw/day.

In the histopathological analysis, minimal bronchiolo-alveolar inflammation in the lung and hyperplasia of squamous cells in the forestomach were observed in males at 150 mg/kg bw/day.

In the recovery study, gasping was transiently observed in satellite females at 150 mg/kg bw/day, and bronchiolo-alveolar inflammation in the lung was observed in males at the same dose at the end of the recovery period. These findings were probably due to benzyl (dimethyl) (octan-1-yl) ammonium chloride entering the trachea by aspiration or other causes.

Based on these results, the no observed adverse effect levels (NOAELs) for repeated-dose toxicity were determined to be 15 mg/kg bw/day in males and 50 mg/kg bw/day in females.

Reproductive and developmental toxicity

In the screening test described above, no adverse effects on reproductive and developmental parameters

were observed up to the highest dose tested. Therefore, the NOAEL for the reproductive and developmental toxicity was determined to be 150 mg/kg bw/day.

Genotoxicity

In a bacterial reverse mutation assay with *Salmonella typhimurium* (*S. typhimurium*) TA100, TA98, TA1535, and TA1537 and *Escherichia coli* (*E. coli*) WP2 *uvrA* conducted in accordance with OECD TG 471 and the Japanese guidelines stated-above, benzyl(dimethyl)(octan-1-yl)ammonium chloride was positive with TA1537 with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster (CHL/IU) cells performed according to OECD TG 473 and the Japanese guidelines, benzyl(dimethyl)(octan-1-yl)ammonium chloride was negative with and without metabolic activation. Therefore, benzyl(dimethyl)(octan-1-yl)ammonium was determined to be mutagenic *in vitro*.

(2) *cis*-3-Hexenyl salicylate (CAS No.: 65405-77-8)

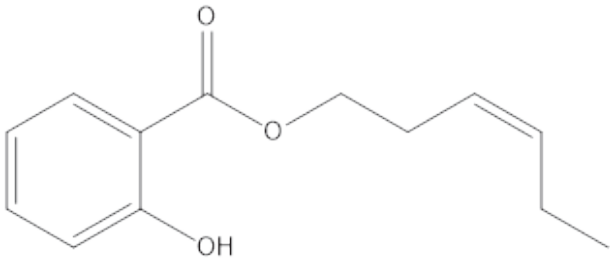

Fig. 2. Structure of cis-3-hexenyl salicylate (CAS No.: 65405-77-8)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with the above-stated Japanese guidelines. Male and female rats (12 animals/sex/dose) were administered *cis*-3-hexenyl salicylate by gavage at 0 (vehicle: corn oil), 40, 120, and 360 mg/kg bw/day. Males were dosed for 42 days, including a 14-day premating and subsequent mating period. Females in the mating group were dosed for 41-49 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Ten additional females were dosed at 0 and 360 mg/kg bw/day as a satellite group for 42 days without mating. Five males and five females were selected from each group for functional, urological, hematological, biochemistry and histopathological examinations at the end of the administration or lactation period. Another five males and satellite females at 0 and 360 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

Deaths were recorded in three mating females at 360 mg/kg bw/day, and one of them exhibited soiled fur and pale skin. In the histopathology of dead animals, acute tubular necrosis in the kidney, vacuolation or necrosis of centrilobular hepatocyte in the liver, increased trabecular bone in the femur, and erosion in the glandular stomach were observed.

Body weights decreased on day 20 of gestation and body weight gain decreased during gestation and lactation in mating females at 360 mg/kg bw/day. In addition, food consumptions decreased on lactation day 4 in mating females at the same dose.

In the urinalysis, water intake increased in males at 360 mg/kg bw/day, which caused an increase in urine volume and a decrease in osmotic pressure.

In the hematology, a decrease in red blood cell count (RBC), increases in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH). and reticulocyte percentage (RET), a prolongation of activated partial thromboplastin (APTT), and a trend toward prolonged prothrombin time (PT) were observed in males at 360 mg/kg bw/day, while a decrease in platelet count was observed in mating females at the same dose.

In the biochemistry, increases in the aspartate aminotransferase (AST), total bile acid (TBA), phospholipids, creatinine (CRNN), inorganic phosphorus (P), albumin (ALB) and albumin/globulin (A/G) ratio were observed in males at 360 mg/kg bw/day. Increases in CRNN and A/G ratio were observed in mating females at the same dose, and increases in the AST, alanine aminotransferase (ALT), triglyceride (TG), P, and A/G ratio, and decreases in glucose (GLU), potassium (K), and chloride (Cl) were observed in satellite females at the same dose.

In the organ weights, decreases in absolute and relative weights of the pituitary were observed in mating females at 360 mg/kg bw/day, while increases in absolute and relative weights of the liver were observed in satellite females at the same dose.

In the gross pathology, dark red focus in the glandular stomach was observed in males and females at 360 mg/kg bw/day.

In the histopathological findings, increased trabecular bone in the femur and, erosion in the glandular stomach were observed in males and females at 360 mg/kg bw/day.

In the recovery study, a decrease in RBC, and increases in MCV and MCH were observed in males at 360 mg/kg bw/day, which were not restored at the end of the recovery period. Increases in absolute and relative weights of the adrenal were observed in satellite females at the same dose.

Based on these results, the NOAEL for repeated-dose toxicity of *cis*-3-hexenyl salicylate was determined to be 120 mg/kg bw/day in males and females.

Reproductive and developmental toxicity

A reproduction and developmental toxicity screening test was conducted with the combined repeated-dose toxicity screening test described above.

For parent animals, trends toward decreased gestation and delivery index, an increase in gestation length, and decreases in number of implantation sites, poor suckling in one dam, and death of all nursing infants in three dams were observed in females at 360 mg/kg bw/day. No reproductive effects were observed in males at the same dose.

For pups, trends toward decreased live birth index and increased number of stillborn offspring, and decreases in number of live offspring, and vestigial tail, complete spinal rachischisis, and exencephaly were observed at 360 mg/kg bw/day. A decrease in viability index on postnatal day (PND) 4, and decreases in body weight and body weight gain in males and females at PND 0 and 4 were observed.

Based on these results, the NOAELs for the reproductive and developmental toxicity of *cis*-3-hexenyl salicylate were determined to be 360 mg/kg bw/day for male parents and 120 mg/kg bw/day for female parents and pups.

Genotoxicity

In a bacterial reverse mutation assay with *S. typhimurium* TA100, TA98, TA1535, and TA1537 and *E. coli* WP2 *uvrA* performed in accordance with OECD TG 471 and the Japanese guidelines stated above, *cis*-3-hexenyl salicylate was negative with and without metabolic activation. In an *in vitro* chromosomal aberration test performed using Chinese hamster (CHL/IU) cells in accordance with OECD TG 473 and the Japanese guidelines, *cis*-3-hexenyl salicylate was also negative with and without metabolic activation. Therefore, *cis*-3-hexenyl salicylate was determined to be nongenotoxic *in vitro*.

(3) Undecanal (CAS No.: 112-44-7)

Fig. 3. Structure of undecanal (CAS No.: 112-44-7)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with the Japanese guidelines stated above. Male and female rats (12 animals/sex/dose) were administered undecanal by gavage at 0 (vehicle: corn oil), 100, 300, and 1,000 mg/kg body weight/day. Males were dosed for 42 days, including a 14-day premating and subsequent mating period. Females in the mating group were dosed for 41-55 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Ten additional females were dosed at 0 and 1,000 mg/kg bw/day as a satellite group 42 days without mating. Five males and five females were selected from each group for functional, urological, hematological, biochemistry and histopathological examinations at the end of the administration or lactation period. Another five males and satellite females at 0 and 1,000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

Sudden death was recorded in one male at 300 mg/kg bw/day although no death was found at 1,000 mg/kg bw/day. The dead animal showed no histopathological effects from undecanal, so the cause of death was not specified.

In clinical observations, transient salivation right after administration was observed in males and satellite females at 1,000 mg/kg bw/day, which was probably due to the irritant property of undecanal (described in the Safety Data Sheet) because there were no neurotoxicological findings.

No effects were observed on the body weight, food consumption, nor hematology in the treatment groups.

In the biochemistry, AST was increased in satellite females at 1,000 mg/kg bw/day.

No effects were observed on organ weights nor in histopathology.

There were no toxicological effects during or at the end of the recovery period.

Based on these results, the NOAELs for repeated-dose toxicity were determined to be 1,000 mg/kg bw/day in males and 300 mg/kg bw/day in females.

Reproductive and developmental toxicity

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

Genotoxicity

In a bacterial reverse mutation assay with *S. typhimurium* TA100, TA98, TA1535, and TA1537 and *E. coli* WP2 *uvrA* performed in accordance with the Japanese guidelines, undecanal was negative with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese hamster (CHL/IU) cells performed in accordance with the Japanese guidelines, undecanal did not induce structural chromosomal aberrations, but caused polyploidy with continuous treatment (24 h). These results suggest that undecanal is not mutagenic but positive for numerical chromosomal aberration *in vitro*.

(4) Methyl 3-methoxypropanoate (CAS No.: 3852-09-3)

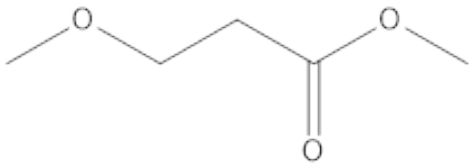

Fig. 4. Structure of methyl 3-methoxypropanoate (CAS No.: 3852-09-3)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with the Japanese guidelines stated above. Male and female rats (12 animals/sex/dose) were administered methyl 3-methoxypropanoate (MMP) by gavage at 0 (vehicle: water for injection), 62.5, 250, and 1,000 mg/kg bw/day. Males were dosed for 42 days, including a 14-day premating period and subsequent mating period. Females in the mating group were dosed for 41–44 days, including the 14-day premating, mating, and gestation periods, and until lactation day 4. Ten additional females were dosed at 0 and 1,000 mg/kg bw/day as a satellite group for 42 days without mating. Five males and five females were selected from each group for functional, urological, hematological, biochemistry and histopathological examinations at the end of the administration or lactation period. Another five males and satellite females at 0 and 1,000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

In clinical observations, transient salivation was found in males and females at 1,000 mg/kg bw/day and was probably caused by the irritation property of MMP because no neurotoxic effects were observed.

Food consumption decreased on administration day 1 in males and satellite females at 1,000 mg/kg bw/day. In mating females receiving the same dose, food consumption tended to decrease on administration day 1 and decreased on lactation day 3.

In the urinalysis, the urine volume increased in males at 1,000 mg/kg bw/day and tended to increase in satellite females. At the same dose, low pH of urine, and tendencies of increases in volume of excreted electrolytes (Na, K, and Cl) and decreases in volume of them (except for Na in females) were observed. Increases in protein, ketone, and Na were also found in females. At the end of the recovery period, the density and volume of electrolytes significantly increased with urinal specific gravity in females.

In the hematology, platelets decreased, PT prolonged, and APTT shortened in satellite females at 1,000 mg/kg bw/day.

Biochemical investigations showed that the TBA in blood increased in males and satellite females and tended to increase in mating females receiving 1,000 mg/kg bw/day. At the highest dose, the total bilirubin also increased in males and satellite females.

Significant increases in lactate dehydrogenase (LDH), GLU, and TG were observed in males at 250 mg/kg bw/day. Tendencies of increases in them were also found in males at 1,000 mg/kg bw/day, and LDH tended to increase in mating females at ≥250 mg/kg bw/day.

In the organ weights, absolute and relative weights of the liver increased in mating and satellite females and tended to increase in males at 1,000 mg/kg bw/day. In addition, tendencies toward increases in absolute and relative weights of the kidneys were observed in males and satellite females at the highest dose.

Based on these findings, the NOAEL for repeated-dose toxicity of MMP was determined to be 62.5 mg/kg bw/day for both males and females.

Reproductive and developmental toxicity

Reproductive and developmental toxicity observations were conducted with the screening test described above.

The length of estrous cycle and gestation prolonged in dams at 1,000 mg/kg bw/day. Decreases in numbers of offspring and live offspring at birth were also observed at the same dose.

Therefore, the NOAEL for reproductive and developmental toxicity was determined to be 250 mg/kg bw/day.

Genotoxicity

A bacterial reverse mutation assay was conducted in accordance with the Japanese guidelines. In this test, the genotoxicity of MMP was negative for *S. typhimurium* TA100, TA98, TA1535, and TA1537 and *E. coli* WP2 *uvrA* with and without metabolic activation.

Conversely, an *in vitro* chromosomal aberration test using CHL/IU cells was also performed with the Japanese guideline. In this test, MMP had no clastogenicity but weakly caused polyploidy with metabolic activation. These results suggest that undecanal is nonmutagenic but weakly positive for numerical chromosomal aberration *in vitro*.

(5) 1-Ethoxy-2-(2-methoxyethoxy) ethane (CAS No.: 1002-67-1)

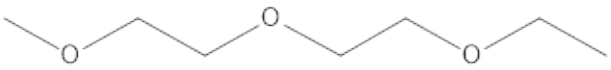

Fig. 5. Structure of 1-ethoxy-2-(2-methoxyethoxy) ethane (CAS No.: 1002-67-1)

Repeated-dose toxicity

A combined repeated-dose toxicity study with a reproduction and developmental toxicity screening test was performed in accordance with the Japanese guidelines stated above. Male and female rats (12 animals/sex/dose) were administered 1-ethoxy-2-(2-methoxyethoxy)ethane (EMEE) by gavage at 0 (vehicle: water for injection), 62.5, 250, and 1,000 mg/kg body weight/day. Males were dosed for 42 days, including a 14-day premating period and subsequent mating period. 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. Ten additional females were dosed at 0 and 1,000 mg/kg bw/day as a satellite group for 42 days without mating. Five males and five females were selected from each group for functional, urological, hematological, biochemistry and histopathological examinations at the end of the administration or lactation period. Another five males and satellite females at 0 and 1,000 mg/kg bw/day were allocated to a recovery group and maintained for 14 days after the administration period.

A decrease in locomotor activity in males and females at 1,000 mg/kg bw/day. Transient salivation was observed in males and mating females during gestation and lactation at the highest dose and was probably caused by EMEE-induced irritation because no neurotoxic effects were found in detailed clinical observations nor functional examinations. The body weight was unaffected except for a decrease on gestation day 20 which was probably related to litter loss or growth inhibition in utero during pregnancy at 1,000 mg/kg bw/day. A decrease in food consumption was observed in males and satellite females at the highest dose at the beginning and end of the administration period, and in dams receiving 250 mg/kg bw/day on lactation day 3.

In the urinalysis, decreases in K and Cl were

observed in males at 1,000 mg/kg bw/day on the end of the administration period, and decreases in urine specific gravity and density of Na, K, and Cl were found in satellite females at the same dose on the end of the recovery period.

Hematologic research showed decreases in hemoglobin and hematocrit in males and satellite females at 1,000 mg/kg bw/day. A decrease in RET was also observed in males at ≥250 mg/kg bw/day. In addition, RET, MCHC, and platelet decreased in satellite females at the highest dose.

In the biochemistry, the total protein in blood decreased and γ-glutamyl transpeptidase increased in males at 1,000 mg/kg bw/day.

The absolute and relative weights of the thymus decreased, whereas the relative weights of the liver and kidneys increased in males and satellite females receiving 1,000 mg/kg bw/day. In males, the absolute and relative weights of the epididymides and the prostate decreased at the same dose. At the end of the recovery period, a decrease in absolute epididymides weight and an increase in relative liver weight were still observed in males at the highest dose.

In the histopathology, the following findings were found at 1,000 mg/kg bw/day. in the thymus, medulla atrophy was found in males and satellite females. In the liver, hypertrophy of centrilobular hepatocytes and ground glass appearance of hepatocytes were observed in males and females; hypertrophy of centrilobular hepatocytes was also observed in males receiving 250 mg/kg bw/day. In the testis, exfoliation of spermatids, multinucleated giant cells, and vacuolation of the germ cell layer were found in the seminiferous tubule. In addition, cell debris and a decreased number of sperm were observed in the epididymis lumen; a decrease in liquid content in the prostate lumen was also found. These lesions in the testis and epididymis were still present at the end of the recovery period and were poorly reversible.

Based on these findings, the NOAEL for the repeated-dose toxicity from EMEE was determined to be 62.5 mg/kg bw/day in males and females.

Reproductive and developmental toxicity

Reproductive and developmental toxicity observations were conducted with the screening test described above.

The estrous cycle and gestation length prolonged in dams receiving 1,000 mg/kg bw/day. Three of 12 females were not pregnant, and implantation index, delivery index for dams decreased. Also decreases in born offsprings, birth index (both offspring and live offspring), and delivery index for offspring were observed. Nursing behavior for live offspring at birth was lacking. These findings resulted in all offsprings deaths before PND 4.

The NOAEL for reproductive and developmental toxicity from EMEE was considered to be 250 mg/kg bw/day.

Genotoxicity

In a bacterial reverse mutation assay with *S. typhimurium* TA100, TA98, TA1535, and TA1537 and *E. coli* WP2 *uvrA* in accordance with the Japanese guidelines, EMEE was negative with and without metabolic activation. In an *in vitro* chromosomal aberration test using CHL/IU cells performed with the Japanese guideline, EMEE had no clastogenicity. Therefore, EMEE is determined to be nongenotoxic *in vitro*.

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