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

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Chemical substances have been used in several products and so are a necessity to our lives. Under the Chemical Substance Control Law, toxicological information on existing chemical substances has been gathered by the Ministry of Health, Labor and Welfare in Japan. To explore whether these chemical substances have an effect on human health, we have assessed the toxicological information of these chemical substances, including the data on repeated-dose toxicity, genotoxicity, and reproduction/developmental toxicity. At this moment, we have reviewed the toxicological information and reported the summary of evaluation results of the following 5 substances: 4-*sec*-butyl-2,6-di-*tert*-butylphenol（CAS: 17540-75-9）, sodium 2-hydroxypropanoate（CAS: 312-85-6）, bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate（CAS: 2915-49-3）, poly(vinylidene fluoride)（CAS: 24937-79-9）, and 6H-Dibenz[c,e][1,2] oxaphosphorin-6-oxide（CAS: 35948-25-5）. The detailed information about the toxicological test of 5 chemical substances is available in Japan Existing Chemical Database.

Keywords: existing chemical substance, JECDB, IUCLID, dossier

## Introduction

Chemical substances have been used in several products including plastics, household goods, cosmetics, pesticides, and pharmaceuticals and are a necessity to our lives. Notwithstanding, there are concerns as regards their adverse effects on human health as well as the environment. In Japan, after the health damage caused by polychlorinated biphenyls（PCBs）, the Chemical Substance Control Law（CSCL）was enacted in the year 1973[1)]. This law was made to put a stop to the environmental pollution by these chemical substances risking human health or the environment in Japan. The said chemical substances which have been on the market after 1973 are known as newly registered chemical substances on the act. Their properties are to be analyzed before the manufacture, import, and use with the safety data submitted by the company. Chemical substances that are already in the market before 1973 are known as existing chemical substances, and the Japanese government has collected the safety data of these substances to evaluate their properties.

Since there are many existing chemical substances used worldwide, the Organization for Economic Co-operation and Development（OECD）had conducted programs called OECD High Production Volume Chemicals Program and later called OECD Cooperative Chemicals Assessment Program（CoCAP）to collect and analyze toxicological data of existing chemical substances by sharing among member countries since the 1990s. The Japanese government has participated in the said programs and submitted initial assessment of documents including toxicological information of approximately 200 out of about 450 existing chemical substances collected by the Ministry of Health, Labor and Welfare（MHLW）. These initial assessments of the documents submitted to the OECD are available for the public at https://hpvchemicals.oecd.org/ui/Search.aspx.

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Because sharing the toxicological information internationally to avoid unnecessary testing is very important, we have continued to publish new toxicological information of remaining existing chemical substances obtained by MHLW even after initial assessment of chemical substances by CoCAP ended in 2013.

We have conducted two processes for the toxicological information to be published. On the one hand, the first process involves reviewing toxicological information of the remaining existing chemical substances collected by the MHLW. On the other hand, the second process involves creating a dossier in English using the International Uniform Chemical Information Database (IUCLID). Each dossier has study data, which has a detailed summary of the methods, results, and conclusions for each. After completing the two processes, we have published each dossier to Japan Existing Chemical Database (JECDB), which is accessible at https://dra4.nihs.go.jp/mhlw_data/jsp/SearchPage.jsp. Prior five reports on the summary information of the assessment of toxicological tests published in JECDB are also available [2-6].

Today, we have reviewed toxicological information and reported the summary of the evaluation results of the succeeding five substances: 4-*sec*-butyl-2,6-di-*tert*-butylphenol (CAS:17540-75-9), sodium 2-hydroxypropanoate (CAS: 312-85-6), bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate (CAS: 2915-49-3), poly(vinylidene fluoride) (CAS: 24937-79-9), and 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide (CAS: 35948-25-5). The results of toxicological studies for repeated-dose toxicity, genotoxicity, and reproduction/developmental toxicity for these chemical substances were secured from existing chemicals survey program carried out by the MHLW for the CSCL.

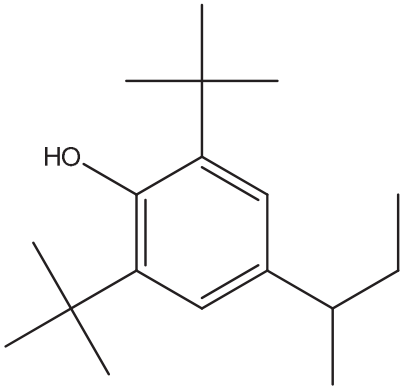


Fig. 1. Chemical structure of 4-*sec*-butyl-2,6-di-*tert*-butylphenol (CAS: 17540-75-9)

### (1) 4-*sec*-Butyl-2,6-di-*tert*-butylphenol (CAS: 17540-75-9)

The repeated-dose toxicity of 4-*sec*-butyl-2,6-di-*tert*-butylphenol was assessed with the use of rats. Male and female rats (6 animals/sex/dose) were administered with 0 [vehicle: corn oil], 15, 60, and 250 mg/kg bw/day of 4-*sec*-butyl-2,6-di-*tert*-butylphenol for 28 days. Six of the 12 animals/sex that have received 0 and 250 mg/kg bw/day were selected to be part of a 14-day recovery group.

No treatment-related deaths were noted for both sexes. Clinical signs have shown that the doses did not affect the manipulative test, body weight, and food consumption. In general appearance, the male and female groups receiving 250 mg/kg bw/day had soft feces. The urinalysis shows the urine pH in females receiving 250 mg/kg bw/day was significantly decreased. Hematological parameters, such as prothrombin time in males in the ≥60 mg/kg bw/day group as well as activated partial thromboplastin time in males in the ≥60 mg/kg bw/day group and in females in the 250 mg/kg bw/day group, were significantly prolonged. Blood chemistry analysis has shown that total cholesterol level in females receiving ≥15 mg/kg bw/day and in males receiving ≥60 mg/kg bw/day and total bilirubin level in both sexes receiving 250 mg/kg bw/day significantly increased. Contrarily, the levels of potassium (K) and inorganic phosphorus (IP) significantly decreased in male rats receiving 250 mg/kg bw/day. A gross pathological examination has shown watery content of cecum in males receiving 60 mg/kg bw/day and in both sexes receiving 250 mg/kg bw/day. Soft feces, watery content of cecum, and decreases of K and IP levels were discovered, suggesting that the digestive tract is affected. There has been significantly increase in the relative weight of the liver of females receiving ≥15 mg/kg bw/day and the absolute weight of the liver of females receiving 250 mg/kg bw/day. Histopathological findings declared a slight hypertrophy of centrilobular hepatocytes in females receiving 250 mg/kg bw/day. These changes were no longer observed after the recovery period, showing that they were reversible. Founded on these effects of the cecum at 60 mg/kg bw/day in males,

the No Observed Adverse Effect Level (NOAEL) for repeated-dose toxicity of 4-*sec*-butyl-2,6-di-*tert*-butylphenol was 15 mg/kg bw/day in rats.

The reproduction/developmental toxicity screening test of 4-*sec*-butyl-2,6-di-*tert*-butylphenol was assessed in rats in accordance to the OECD test guideline (TG) 421. In this study, 4-*sec*-butyl-2,6-di-*tert*-butylphenol was administered via gavage at 0 [vehicle: corn oil], 12, 60 and 300 mg/kg bw/day. Males (12/dose) were then treated for 42 days, which include a 14-day premating period and subsequent mating period, while females (12/dose) were treated for 42–46 days, including 14-day premating, mating, and gestation periods until lactation day 4. Two of the female rats treated with 300 mg/kg bw/day died during late pregnancy. Among these dead females, hypothermia and emaciation were seen, and malnutrition, enlargement of the liver, distention of the cecum, and miniaturization of the thymus were observed in gross pathology. Histopathological findings have shown hypertrophy and vacuolation of centrilobular hepatocytes, hypertrophy of bile duct epithelial cells, and atrophy of thymus in the dead females. At 300 mg/kg bw/day, soft feces were seen in some males and females. Additionally, hypothermia, emaciation, pale skin, and vaginal hemorrhage at lactation period were observed in two dams. All pups of those two dams died until lactation day 2. After 2 weeks of administration of 300 mg/kg bw/day in males, lower body weight was noted. At 60 mg/kg bw/day, there were several effects on the liver, including increased liver weight and hypertrophy of centrilobular hepatocytes, in both males and females. So the NOAEL for 42–46 day repeated-dose toxicity of 4-*sec*-butyl-2,6-di-*tert*-butylphenol was 12 mg/kg bw/day in rats, based on limited evaluation of repeated-dose toxicity in this study, which is similar to the 28-day repeated-dose NOAEL (15 mg/kg bw/day).

A bacterial reverse mutation assay with the use of *Salmonella typhimurium* (*S. typhimurium*) TA100, TA1535, TA98, and TA1537 and *Escherichia coli* (*E. coli*) WP2*uvrA* had a negative result for 4-*sec*-butyl-2,6-di-*tert*-butylphenol, both with and without metabolic activation. An *in vitro* chromosome aberration test with the use of Chinese hamster lung (CHL/IU) cells has shown that 4-*sec*-butyl-2,6-di-*tert*-butylphenol was equivocal (weakly positive) for numerical aberration and structural aberration with metabolic activation.

In the above-described reproduction/developmental toxicity screening test (OECD TG 421), there were no effects on fertility but a tendency of lowing in the delivery index, the number of liveborn, and live birth index and the tendency of high stillborn rate were observed in 300 mg/kg bw/day group. The tendency of low viability index on postnatal day 4 was seen in the 300 mg/kg bw/day group. Because there was no effect of the test substance in the parental males and pup at 300 mg/kg bw/day, the NOAEL of paternal and developmental toxicities was 300 mg/kg bw/day group. On the other hand, as seen on the effects on general condition of dams and delivery at 300 mg/kg bw/day, the NOAEL of the maternal toxicity was 60 mg/kg bw/day. In conclusion, the overall NOAEL for the reproductive/developmental toxicity of 4-*sec*-butyl-2,6-di-*tert*-butylphenol in this study was 60 mg/kg bw/day.

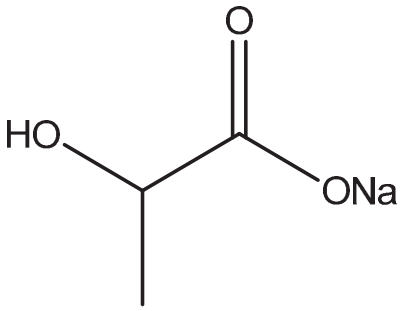


Fig. 2. Chemical structure of sodium 2-hydroxypropanoate (CAS: 312-85-6)

### (2) Sodium 2-hydroxypropanoate (CAS: 312-85-6)

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was performed according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with sodium 2-hydroxypropanoate via oral gavage at doses of 0 [vehicle: water for injection], 100, 300, and 1,000 mg/kg bw/day. Males (12/dose) were treated with sodium 2-hydroxypropanoate for 42 days, with a 14-day premating period and subsequent mating period, while females (12/dose) were treated for 41–50 days, with 14-day premating, mating, and gestation periods until lactation day 4. Among the 12 males treated with 0 and 1,000 mg/kg bw/day, 5 of them were assigned as the recovery group. Additional 10 females treated with 0 and 1,000 mg/kg bw/day were

assigned as the satellite group and treated with sodium 2-hydroxypropanoate for 42 days, without mating, and then examined after a 14-day recovery period.

No deaths were recorded, and there were no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, hematology, blood chemistry, and gross pathological findings resulting from the treatment in any of the dose groups for both sexes at the end of the treatment and recovery periods. At the end of the administration period, thyroid hormone ($T_4$ and TSH) levels were significantly increased in males receiving 1,000 mg/kg bw/day. Both absolute weight and relative weight of the thymus and spleen were also significantly increased in the mating group females receiving 1,000 mg/kg bw/day. Histopathological changes were also seen in the forestomach, which include slight/mild hyperplasia of squamous cells, in males receiving ≥300 mg/kg bw/day, and mating and non-mating females receiving 1,000 mg/kg bw/day at the end of the administration period. These histopathological findings in the forestomach indicate that there is a mucosal irritation by the test substance. Since these changes lessen or disappear at the end of the recovery period, they are thought to be reversible. Because there are effects on the forestomach at 300 mg/kg bw/day in males, the NOAEL for repeated-dose toxicity of sodium 2-hydroxypropanoate was 100 mg/kg bw/day in rats.

A bacterial reverse mutation assay with the use of *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA* indicated a negative result for sodium 2-hydroxypropanoate, both with and without metabolic activation. An *in vitro* chromosome aberration test with the use of CHL/IU cells has shown sodium 2-hydroxypropanoate to be negative both with and without metabolic activation. These results indicate that sodium 2-hydroxypropanoate is nongenotoxic *in vitro*.

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was performed according to OECD TG 422 as described previously; mortalities were not recorded with any dose in the treatment period. No effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity were indicated up to the highest dose. Because there was no effect at 1,000 mg/kg bw/day, the NOAEL for the reproduction and development toxicity was 1,000 mg/kg bw/day in rats.

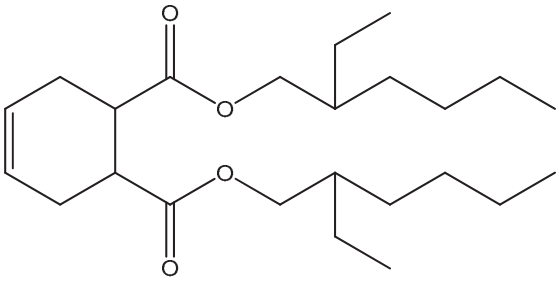

**Fig. 3. Chemical structure of bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate (CAS: 2915-49-3)**

**(3) Bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate (CAS: 2915-49-3)**

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was done according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate via oral gavage at doses of 0 [vehicle: corn oil], 30, 100, and 300 mg/kg bw/day. Males (12/dose) were administered with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, which include a 14-day premating period and a subsequent mating period, while females (12/dose) were treated for 41–46 days, which include 14-day premating, mating, and gestation periods until lactation day 4. Among the 12 males administered with 0 and 300 mg/kg bw/day, 5 were assigned as the recovery group. Additionally, 10 females administered with 0 and 300 mg/kg bw/day were assigned as a satellite group and treated with bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate for 42 days, without mating, and assessed after a 14-day recovery period.

No deaths were recorded, and there are no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, blood chemistry, blood hormone ($T_3$, $T_4$, and TSH), and gross pathological findings resulting from the treatment in any of the dose groups for both sexes at the end of the treatment and recovery periods. The level of white blood cell, lymphocyte, neutrophil, and large unstained cells was significantly decreased

in males receiving 300 mg/kg bw/day at the end of the administration period. The absolute and relative weights of liver were significantly increased as well in both sexes receiving 300 mg/kg bw/day at the end of the administration period. There was also significant increase in absolute and relative weights of kidney in the males receiving 300 mg/kg bw/day at the end of the administration period. Histopathological analysis has indicated a slight hypertrophy of centrilobular hepatocytes in males receiving 300 mg/kg bw/day and in females 100 and 300 mg/kg bw/day at the end of the administration period. Since these changes lessen or disappear at the end of the recovery period, they are thought to be reversible. Based on the effects of the liver at 100 mg/kg bw/day in females, the NOAEL for repeated-dose toxicity of bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate was 30 mg/kg bw/day in rats.

A bacterial reverse mutation assay with the use of *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA* has shown a negative result for bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate, both with and without metabolic activation. An *in vitro* chromosome aberration test with the use of CHL/IU cells has shown that bis(2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate was negative with or without metabolic activation. These results indicated that bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate is nongenotoxic *in vitro*.

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was performed according to OECD TG 422 as explored above; no mortalities were recorded with any dose during the treatment period. There were also no effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity up to the highest dose. Because there was no effect observed at 300 mg/kg bw/day administration, the NOAEL for the reproduction and development toxicity was 300 mg/kg bw/day in rats.

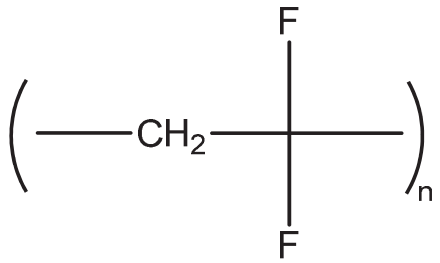


Fig. 4. Chemical structure of poly(vinylidene fluoride) (CAS: 24937-79-9)

### (4) Poly(vinylidene fluoride) (CAS: 24937-79-9)

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was done according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with poly(vinylidene fluoride) via oral gavage at doses of 0 [vehicle: corn oil], 100, 300, and 1,000 mg/kg bw/day. Males (12/dose) were treated with poly (vinylidene fluoride) for 42 days, which include a 14-day premating period and a subsequent mating period, while females (12/dose) were treated for 42–46 days, including 14-day premating, mating, and gestation periods until lactation day 4. Among the 12 males that were treated with 0 and 1,000 mg/kg bw/day, 5 were assigned as the recovery group. Additional 10 females administered with 0 and 1,000 mg/kg bw/day were assigned as a satellite group and treated with poly (vinylidene fluoride) for 42 days, with no mating, and examined after a 14-day recovery period.

No deaths were recorded, and there are no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, hematology, blood chemistry, gross pathological findings, and histopathological findings as a result of treatment in any of the dose groups for both males and females at the end of the treatment and recovery periods. Although absolute and relative weights of pituitary were significantly increased in the mating group females receiving 1,000 mg/kg bw/day at the end of the administration period, these changes were not considered to be adverse effects since there were no histological abnormalities and effect on endocrine organs observed. Since there is no toxicological alteration, the NOAEL for repeated-dose toxicity of poly(vinylidene fluoride) was 1,000 mg/kg bw/day in rats.

A bacterial reverse mutation assay using *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA* has shown negative results for poly (vinylidene fluoride) both with and without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells has indicated that poly(vinylidene fluoride) was negative with or without metabolic

activation. These results have shown that poly (vinylidene fluoride) is nongenotoxic *in vitro*.

In the combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described previously, no mortalities were recorded with any dose in the treatment period. There were also no effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity up to the highest dose. Since the effects were not even observed at 1,000 mg/kg bw/day administration, the NOAEL for the reproduction and development toxicity was 1,000 mg/kg bw/day in rats.

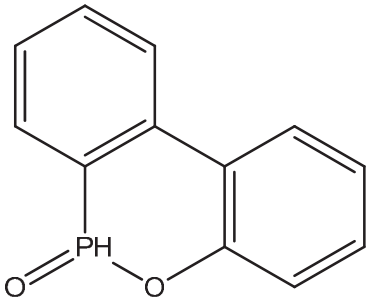


Fig. 5. Chemical structure of 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide (CAS: 35948-25-5)

### (5) 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide (CAS: 35948-25-5)

A combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test was done according to OECD TG 422. Male and female rats (12 animals/sex/dose) were administered with 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide via oral gavage at doses of 0 [vehicle: corn oil], 100, 300, and 1,000 mg/kg bw/day. Males (12/dose) were then treated with 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide for 42 days, which include a 14-day premating period and a subsequent mating period, while females (12/dose) were treated for 41–46 days, which include a 14-day premating, mating and gestation periods until lactation day 4. Among the 12 males administered with 0 and 1,000 mg/kg bw/day, 5 were assigned as recovery group. Additional 10 females treated with 0 and 1,000 mg/kg bw/day were assigned as a satellite group and treated with 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide for 42 days, with no mating, and examined after a 14-day recovery period.

No deaths were recorded, and no changes in clinical signs, manipulative test, grip strength, motor activity, body weight, food consumption, urinalysis, hematology, blood chemistry as a result of treatment in any of the dose groups for both males and females at the end of the treatment and recovery periods. There was a decrease in body weight gain in males receiving 1,000 mg/kg bw/day after 2 weeks of administration, and a statistically significant decreased body weight gain was observed in the mating group females receiving 1,000 mg/kg bw/day in the gestation period. The absolute and relative weights of the thymus were significantly decreased in the satellite group females receiving 1,000 mg/kg bw/day at the end of the administration period. In the gross pathological examination of males receiving ≥ 300 mg/kg bw/day, a raised and dark red forestomach was seen. Additionally, there was thickening of the limiting ridge of the forestomach in females receiving 100 mg/kg bw/day at the end of the administration period. Histopathological findings show an erosion/ulcer and edema in the mucosa/submucosa of the forestomach in females receiving 100 mg/kg bw/day and both males and females receiving ≥300 mg/kg bw/day, and degeneration/necrosis of squamous cells of the forestomach was indicated in males receiving 100 mg/kg bw/day and both males and females receiving ≥300 mg/kg bw/day. There was also a hyperplasia of squamous cells of the forestomach in both males and females at ≥100 mg/kg bw/day. These histopathological findings in the forestomach mean that there is a mucosal irritation by the test substance. Single-cell necrosis and diffuse hyperplasia of cecum mucosa were seen in both males and females at ≥ 300 mg/kg bw/day. Since the changes observed in the organ weight and histopathological examination were lessened or disappeared at the end of the recovery period, they are thought to be reversible. With these effects of the forestomach at 100 mg/kg bw/day in males and females, the Lowest Observed Adverse Effect Level (LOAEL) for repeated-dose toxicity of 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide was 100 mg/kg bw/day in rats.

A bacterial reverse mutation assay with the use of *S. typhimurium* TA100, TA1535, TA98, and TA1537 and *E. coli* WP2*uvrA* has shown negative results for 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide, both with and without metabolic activation. An *in vitro*

chromosome aberration test that used CHL/IU cells (OECD TG 473) has shown that 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide was also negative, with or without metabolic activation. These results show that 6H-Dibenz[c,e][1,2]oxaphosphorin-6-oxide is nongenotoxic *in vitro*.

The combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) described above indicated that there were no mortalities with any dose during the treatment period. No effects on reproductive toxicity (fertility and reproductive organs) and developmental toxicity up to the highest dose were recorded. Since the effects were not even observed at 1,000 mg/kg bw/day, the NOAEL for the reproduction and development toxicity was 1,000 mg/kg bw/day in rats.

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