Revision of the Cabinet Order of the Law Concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc.

October 2007
Ministry of Health, Labour and Welfare
Ministry of Economy, Trade and Industry
Ministry of the Environment

The Ministry of Health, Labour and Welfare; the Ministry of Economy, Trade and Industry; and the Ministry of the Environment promulgated the revised Cabinet Order of the Law Concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc. on October 31, 2007.

The revision was made to designate *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-*［CAS No: 3846-71-7］as a Class I Specified Chemical Substance, and to designate the products prohibited from importation when this substance is used in them.

Background

The Ministry of Health, Labour and Welfare; the Ministry of Economy, Trade and Industry; and the Ministry of the Environment (hereinafter referred to as "the three Ministries") implement chemical safety policy based on the "Law concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc." (hereinafter referred to as "the Law"), in order to prevent environmental pollution by chemical substances that have persistent and chronically toxic properties. The Law asks the three Ministries to designate substances with non-biodegradability, a high degree of bioaccumulation, and chronic toxicity as "Class I Specified Chemical Substances," via the Cabinet Order of the Law concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc. (hereinafter referred to as "the Cabinet Order"), and restricts the production, import, and use of those substances. The Law also prohibits the importation of products using "Class I Specified Chemical Substances" when those products are on the list of prohibited products in Article 3 of the Cabinet Order.

Relevant councils of the three Ministries had held deliberations on the safety of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-*［CAS No: 3846-71-7］(hereinafter referred to as "the substance") based on results of testing of the substance, and had concluded that the substance exhibits non-biodegradability, a high degree of bioaccumulation, and chronic toxicity, thus requiring it to be designated as a Class I Specified Chemical Substance. The councils had also required the designation of products to be prohibited from importation when the substance is used in them.

Outline of the revision of the Cabinet Order

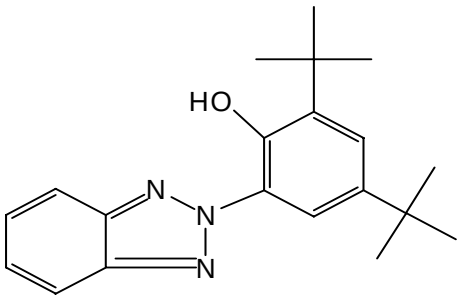
In response to the conclusion of the councils, the three Ministries promulgated the revised Cabinet Order on October 31, in order to designate the substance as a Class I Specified Chemical Substance (Article 1 of the Cabinet Order), and to designate products such as paints and glue as products prohibited from importation when the substance is used in them (Article 3 of the Cabinet Order).

Enforcement date

The revision related to Article 1 of the Cabinet Order: November 10, 2007
The revision related to Article 3 of the Cabinet Order: May 1, 2008

Physical-chemical properties, biodegradation, bioaccumulation, and toxicity of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-*

1. Structural formula



2. CAS No.：3846-71-7
3. Molecular formula：323.44
4. Physical-chemical properties (provided by The Ministry of Economy, Trade and Industry : METI)
   1) Melting point：154.6 ℃
   2) Boiling point：－
   3) Water solubility：<10 mg/L
   4) Vapor pressure：－
   5) 1-Octanol / water partition coefficient：≧5.50
5. Usage：an UV absorber for a variety of applications including glue, paints, and plastics
6. Biodegradation (provided by METI)

METHOD

Guideline: OECD TG 301C(MITI Method)
GLP: Yes
Year: 1996 (published year)
Cultivation period: 28 days
Test substance concentration: 100 mg/L
Activated sludge concentration: 30 mg/L
Analysis apparatus: HPLC

RESULTS

Biodegradability:

-	Biodegradability (%)			
Biodegradability by TOC	1	0	0	0 (Average)
Biodegradability by HPLC	0	0	1	0 (Average)

7. Bioaccumulation (provided by METI)

METHOD

Guideline: OECD 305C (MITI Method)

GLP: Yes

Year: 1998 (published year)

Test system: Flow-through (100-L glass tank, 1155 L/day)

Fish species: Carp (*Cyprinus carpio*)

Exposure period: Level 1 and 2 14 weeks

Level 3 10 weeks

Analysis apparatus: HPLC

Lipid content of the test fish:

Level 1 and 2 3.7% (average lipid content)

Level 3 3.6 % (average lipid content)

Nominal concentration in test water:

(μg/L)

Level	Test substance	Dispersant	
		HCO-40	Olive oil
1	10	200	100
2	1	20	10
3	0.1	2	1

RESULTS

Bio-concentration factor:

Level	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks
1	365 429	1050 1070	1020 952	1260 1150	2250 1570	703 1510	1540 1340
2	1380 1820	3320 4640	3970 3340	3080 5570	6200 7200	8180 7390	4020 4720
3	2960 4910	5890 4960	5360 6920	8530 10000	7740 9600		

8. Repeated dose 28-day oral toxicity study of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-*［CAS No: 3846-71-7］in rats (Provided by The Ministry of Health, Labour and Welfare: MHLW)

The repeated dose toxicity study of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-* was conducted according to an OECD TG407 [Repeated Dose 28-day Oral Toxicity Study in Rodent] under GLP. *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-* was suspended in corn oil. Crj:CD(SD)IGS rats were given *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-* by gavage at a dose of 0 (vehicle: corn oil), 0.5, 2.5, 12.5 or 62.5 mg/kg bw/day for 28 days in males and females. The initial numbers of rats were 10/sex at 0 and 62.5 mg/kg bw/day, and 5/sex at 2.5 and 12.5 mg/kg bw/day. Five rats/sex from each group were killed on day 29, and remaining 5 rats/sex at 0 and 62.5

mg/kg bw/day were kept without treatment for 14 days (recovery period). No deaths or toxicological signs were observed in any group. An increase in relative weight of the liver and hypertrophy of the liver were noted in males at 0.5 mg/kg bw/day and higher and females at 12.5 mg/kg bw/day and higher. The relative weight of the kidney was increased in males at 62.5 mg/kg bw/day. Histopathological examinations of the liver revealed hypertrophy of the hepatocytes, vacuolar degeneration of the hepatocytes, increased mitosis and/or bile duct proliferation in males at 0.5 mg/kg bw/day and higher and females at 12.5 mg/kg bw/day and higher. Hypertrophy of the hepatocytes was accompanied by necrosis and degeneration of the liver. Focal necrosis and pigment deposition in the liver were also observed in males. Cell infiltration in the heart in males at 2.5 mg/kg bw/day and higher and females at 12.5 mg/kg bw/day and higher, myocardial degeneration in both sexes at 12.5 mg/kg bw/day and higher, follicular cell proliferation in the thyroid and tubular epithelial hypertrophy in the kidney at 12.5 mg/kg bw/day and higher in males and 62.5 mg/kg bw/day in females were noted. In hematological examinations, reductions in hematocrit value, hemoglobin concentration and number of red blood cells at 2.5 mg/kg bw/day and in mean corpuscular hemoglobin concentration at 12.5 mg/kg bw/day were found in males. Blood biochemical examinations revealed increased levels of GPT at 12.5 mg/kg bw/day and higher in males and 62.5 mg/kg bw/day in females, of ALP at 12.5 mg/kg bw/day and higher in males, and of GOT at 62.5 mg/kg bw/day in males, of glucose at 2.5 mg/kg bw/day and higher in males and 62.5 mg/kg bw/day in females, and of albumin at 12.5 mg/kg bw/day and higher in males, and elevated ratio of albumin/globulin at 0.5 mg/kg bw/day and higher in males and 62.5 mg/kg bw/day in females. Most of these toxicological changes were also noted in *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)*--treated male rats after the recovery period. These data indicate that the toxic effects of this chemical principally affects on the liver and male rats are more susceptible to toxic effects of this chemical than female rats. In conclusion, the NOELs for repeated dose toxicity are considered to be less than 0.5 mg/kg bw/day in male rats and 2.5 mg/kg bw/day in female rats.

9. Chronic toxicity study of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)*-［CAS No: 3846-71-7］in rats (Provided by MHLW)

The chronic toxicity study of *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)*- was conducted according to an OECD TG452 [Chronic Toxicity Studies] under GLP. *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)*- was suspended in corn oil. Crj:CD(SD)IGS rats (10/sex/group) were given *Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)*- by gavage at a dose of 0 (vehicle: corn oil), 0.1, 0.5 or 2.5 mg/kg bw/day in males and at a dose of 0 (vehicle: corn oil), 0.5, 2.5 or 12.5 mg/kg bw/day in females for 52 weeks. No deaths or toxicological signs were observed in any group. Increases in absolute and relative weights of the liver were found at 0.5 mg/kg bw/day and higher in males and 12.5 mg/kg bw/day in females. The relative weight of the kidney was increased at 2.5 mg/kg bw/day in males. Histopathological examinations of the liver revealed hypertrophy of the hepatocytes and altered hepatocellular foci of the clear cell type at 0.5 mg/kg bw/day and higher, and cystic degeneration and lipofuscin deposition at 2.5 mg/kg bw/day in males. Hypertrophy of the hepatocytes was also observed in females at 12.5 mg/kg bw/day. In hematological examinations, an increased number of platelets at 2.5 mg/kg bw/day in males and 12.5 mg/kg bw/day in females, reduced number of red blood cells at 0.5 mg/kg bw/day and higher in males and decreased hematocrit value at 2.5 mg/kg bw/day in males were noted. Blood biochemical examinations revealed increased levels of ALP, higher ratio of albumin/globulin, decreased levels of globulin and increased levels of albumin at 0.5

mg/kg bw/day and higher, and increased levels of blood urea nitrogen at 2.5 mg/kg bw/day in males. Increased levels of ALP and glucose and reduced levels of total bilirubin were observed at 12.5 mg/kg bw/day in females. An increased osmotic pressure of the urine was found at 0.5 mg/kg bw/day and higher in males, and an increased urinary volume and decreased osmotic pressure of the urine were found at 12.5 mg/kg bw/day in females. The toxicological findings observed in this study were similar to those noted in the 28-day oral toxicity study of this chemical in rats. In conclusion, the NOELs for 52-weeks repeated dose toxicity are considered to be 0.1 mg/kg bw/day in male rats and 2.5 mg/kg bw/day in female rats.