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Chemical Category	BUTYL METHACRYLATE & 2-ETHYLHEXYL METHACRYLATE		

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METHACRYLATE PRODUCERS ASSOCIATION, INC.
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2001 MAY 17 11:11:31

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Re: TSCA Section 8(e) Submission
Butyl Methacrylate (CAS No. 97-88-1)
2-Ethylhexyl Methacrylate (CAS No. 688-84-6)



88010000136

Dear Sir/Madam:

The Methacrylate Producers Association, Inc. ("MPA") has recently received the enclosed abstracts of studies conducted on butyl methacrylate and 2-ethylhexyl methacrylate.

For both chemicals, the enclosed abstracts report on oral toxicity studies in rats that were conducted according to OECD Guidelines No. 471 and 472. Mutagenicity studies were also undertaken. These abstracts were obtained as part of a joint effort among MPA, the CEFIC Methacrylates Sector Group and certain Japanese chemical producers for the SIDS and ICCA programs. Accordingly, these studies and other data will be included in the documents that will be presented later as our consortium fulfills its obligations in the SIDS and ICCA programs. While we are unable, given the sparse information available, to express an opinion as to whether these findings represent a significant risk for health or the environment, this is to our knowledge the first report of the various noted effects.

This submission is being made on behalf of the MPA member companies: CYRO Industries, ATOFINA Chemicals, Inc., INEOS Acrylics, Inc., and Rohm and Haas Company. Nothing in this letter is considered confidential business information of MPA or its members.

If you have any questions regarding this submission please contact me at (703) 327-6276 or via e-mail at ehunt@loudoun.com.

Sincerely,

Elizabeth K. Hunt
Executive Director

2001 MAY 31 4:11:40

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Butyl methacrylate

ブチルメタクリレート

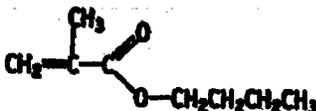
[CAS No. 97-88-1]

Methacrylic acid butyl ester

メタクリル酸ブチルエステル

Molecular formula: $C_9H_{14}O_2$

Molecular weight: 142.20



<Physical Properties>

Appearance	clear colorless liquid
Boiling Point (bp)	100-103°C
Vapor Pressure (vp)	25-52 Torr (72-85°C)
Melting point (mp)	60°C (F)
Density	0.89 g/ml
Solubility in Water	slightly soluble

ABSTRACT

Butyl methacrylate was studied for oral toxicity in rats in an OECD combined repeat dose and reproductive/developmental toxicity screening test at doses of 0, 30, 100, 300 and 1000 mg/kg/day.

With regard to repeat dose toxicity in males, weight gain depression and a decrease in food consumption were observed at a dose of 1000 mg/kg. Urinary examination revealed increases in ketone bodies and occult blood, and hematological and blood chemical examinations showed increases in prothrombin time and urea nitrogen at a dose of 1000 mg/kg. Absolute and relative weights of the spleen were decreased at a dose of 100 mg/kg or more, and relative kidney weights were increased at a dose of 1000 mg/kg. Histopathological examination revealed atrophy of the splenic red pulp at doses of 100 mg/kg or more. The kidney showed no histopathological abnormalities attributable to the test substance. In females, there were weight gain depression and a decrease in food consumption at a dose of 1000 mg/kg. Atrophy of the red pulp in the spleen was also observed histopathologically at a dose of 1000 mg/kg. The NOELs for repeat dose toxicity are considered to be 30 mg/kg/day for males and 300 mg/kg/day for females. In terms of reproductive and developmental toxicity, there were decreases in numbers of corpora lutea and implantations in the parental females. The test substance showed no effects on any reproductive parameters of the parental males or developmental parameters of the offspring. The NOELs for reproductive and developmental toxicity are considered to be 1000 mg/kg/day for the parental males and offspring, and 300 mg/kg/day for the parental females.

Butyl methacrylate was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvrA*, with or without an exogenous metabolic activation system.

Butyl methacrylate did not induce structural chromosomal aberrations or polyploidy in CHL cells, with or without an exogenous metabolic activation system.

SUMMARIZED DATA FROM THE STUDIES

1. Repeat Dose and Reproductive/Developmental Toxicity¹⁾

Purity	: 99.6 %
Test species/strain	: Rat/Crj:CD(SD)
Test method	: OECD Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test
Route	: Oral (gavage)
Doses	: 0(vehicle), 30, 100, 300, 1000 mg/kg/day
Number of animals/group	: Males, 10; females, 10
Vehicle	: Sesame oil
Administration period	: Males, 44 days Females, from 14 days before mating to day 3 of lactation
Terminal kill	: Males, 45 days Females, day 4 of lactation
GLP	: Yes

Test results:

<Repeat Dose Toxicity>

In males, there were weight gain depression and a decrease in food consumption at a dose of 1000 mg/kg. Urinary examination revealed increases in ketone bodies and occult blood, and hematological and blood chemical examinations showed increases in prothrombin time and urea nitrogen at a dose of 1000 mg/kg. Absolute and relative weights of the spleen were decreased at a dose of 100 mg/kg or more, and relative kidney weights were increased at a dose of 1000 mg/kg. Histopathological examination revealed atrophy of the splenic red pulp at doses of 100 mg/kg or more. The kidneys showed no histopathological abnormalities attributable to the test substance.

In females, there were weight gain depression and a decrease in food consumption at a dose of 1000 mg/kg. Atrophy of the red pulp in the spleen was also observed histopathologically at a dose of 1000 mg/kg.

The NOELs for repeat dose toxicity are considered to be 30 mg/kg/day for males and 300 mg/kg/day for females.

<Reproductive and developmental toxicity>

There were decreases in numbers of corpora lutea and implantations in the parental females. The test substance showed no effects on any reproductive parameters of the parental males or developmental parameters of the offspring.

The NOELs for reproductive and developmental toxicities are considered to be 1000 mg/kg/day for the parental males and offspring, and 300 mg/kg/day for the parental females.

2. Genetic Toxicity

2-1. Bacterial test²⁾

Purity	: 99.6 %
Test species/strains	: <i>S. typhimurium</i> TA100, TA1535, TA98, TA1537 <i>E. coli</i> WP2 <i>uvrA</i>
Test method	: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guidelines No. 471 and 472
Procedures	: Pre-incubation method

Solvent	: DMSO
Positive controls	: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98 and WP2 <i>uvrA</i>), Sodium azide (TA1535), 9-Aminocridine hydrochloride (TA1537) +S9 mix: 2-Aminanthracene (all strains)
Doses	: -S9 mix: 9.77, 19.5, 39.1, 78.1, 156 and 313 $\mu\text{g}/\text{plate}$ (TA100, TA1535, TA98 and TA1537); 9.77, 19.5, 39.1, 78.1, 156, 313 and 625 $\mu\text{g}/\text{plate}$ (WP2 <i>uvrA</i>) +S9 mix: 9.77, 19.5, 39.1, 78.1, 156, 313 and 625 $\mu\text{g}/\text{plate}$ (TA100); 19.5, 39.1, 78.1, 156, 313, 625 and 1250 $\mu\text{g}/\text{plate}$ (TA1535, TA1537 and WP2 <i>uvrA</i>); 9.77, 19.5, 39.1, 78.1, 156 and 313 $\mu\text{g}/\text{plate}$ (TA98)
S9	: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test	: 3
Number of replicates	: 2
GLP	: Yes

Test results:

This chemical did not induce gene mutations in the *S. typhimurium* and *E. coli* strains.

Toxicity was observed at a concentration of 156 $\mu\text{g}/\text{plate}$ in the five strains without an S9 mix, and at 313 $\mu\text{g}/\text{plate}$ or greater (TA100, TA1535, TA98, TA1537) and 625 $\mu\text{g}/\text{plate}$ or greater (WP2 *uvrA*) with an S9 mix.

Genetic effects:

S. typhimurium TA100, TA1535, TA98 and TA1537

	+	?	-
Without metabolic activation:	[]	[]	[*]
With metabolic activation:	[]	[]	[*]

E. coli WP2 *uvrA*

	+	?	-
Without metabolic activation:	[]	[]	[*]
With metabolic activation:	[]	[]	[*]

2-2. Non-bacterial *in vitro* test (chromosomal aberration test)²⁾

Purity	: 99.6 %
Type of cell used	: Chinese hamster lung (CHL) cells
Test method	: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guideline No. 473
Solvent	: DMSO
Positive controls	: -S9 mix, Mitomycin C +S9 mix, Cyclophosphamide
Doses	: -S9 mix (continuous exposure): 0, 178, 355, 710, 1420 $\mu\text{g}/\text{mL}$ -S9 mix (short-term exposure): 0, 178, 355, 710, 1420 $\mu\text{g}/\text{mL}$ +S9 mix (short-term exposure): 0, 355, 710, 1420 $\mu\text{g}/\text{mL}$
S9	: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test	: 2
GLP	: Yes

Test results:

This chemical did not induce structural chromosomal aberrations in the absence or presence of an exogenous metabolic activation system.

Genetic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
Without metabolic activation:	[]	[]	[*]	[]	[]	[*]
With metabolic activation:	[]	[]	[*]	[]	[]	[*]

- 1) The tests were performed by the Research Institute for Animal Science in Biochemistry and Toxicology, 3-7-11 Hashimoto-dai, Sagami-hara-shi, Kanagawa 229-1132, Japan. Tel +81-42-762-2775 Fax +81-42-762-7979
- 2) The tests were performed by the Biosafety Research Center, Foods, Drugs and Pesticides (An-pro Center), Japan, 582-2 Shiohinden Arakama, Fukuda-cho, Iwata-gun, Shizuoka, 437-1213, Japan. Tel +81-539-68-1265 Fax +81-539-68-1393

2-Ethylhexyl methacrylate

2-エチルヘキシルメタクリレート

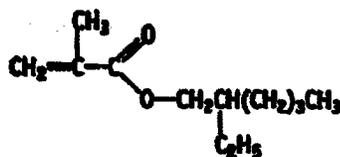
[CAS No. 688-84-6]

Methacrylic acid 2-ethylhexyl ester

メタクリル酸 2-エチルヘキシル

Molecular formula: $C_{18}H_{34}O_2$

Molecular weight: 198.94



<Physical Properties>

Appearance	colorless liquid
Boiling Point (bp)	120°C (18mm)
Vapor Pressure (vp)	non available
Melting point (mp)	non available
Density	0.884 (20°C)
Solubility in Water	non available

ABSTRACT

A single oral dose toxicity test revealed an LD_{50} value of more than 2000 mg/kg for both sexes.

2-Ethylhexyl methacrylate was studied for oral toxicity in rats in an OECD combined repeat dose and reproductive/developmental toxicity screening test at doses of 0, 30, 100, 300 and 1000 mg/kg/day. One female died in the 1000 mg/kg group (12 animals of each sex).

In the males, the absolute kidney weights and the relative pituitary, liver and kidney weights were increased in the 300 and 1000 mg/kg groups. Suppression of body weight gain, decreased food consumption, RBC, hemoglobin, hematocrit, WBC and total protein, and increased GOT, GPT, A/G ratio, BUN and Cl_2 as well as focal necrosis in the liver and decreased extramedullary hematopoiesis in the spleen were seen in the 1000 mg/kg group. In the females, the relative kidney weights were increased in the 100 mg/kg or more groups. Suppression of body weight gain during the pre-mating, pregnancy and lactation periods and decrease in food consumption during the pre-mating period, atrophy of the thymus, increased absolute kidney, relative thyroid and liver weights, and decreased extramedullary hematopoiesis in the spleen and focal malacia in the medulla oblongata were seen in the 1000 mg/kg group. The NOELs for repeat dose toxicity are considered to be 100 mg/kg for males, and 30 mg/kg for females.

With regard to reproductive/developmental toxicity, three of the seven females lost their pups in the 1000 mg/kg group. Numbers of corpora lutea and implantation scars were decreased in the 1000 mg/kg group. The NOELs for reproductive performance are considered to be 1000 mg/kg for males, and 300 mg/kg for females.

With regard to pups, decreased numbers of live pups born were seen in the 300 and 1000 mg/kg groups. Decreased birth, live birth and viability indices, and decreased body weights of both sexes on day 0 and day 4 after birth were seen in the 1000 mg/kg group. The NOEL for pup development is

considered to be 100 mg/kg.

2-Ethylhexyl methacrylate was not mutagenic in *Salmonella typhimurium*: TA1538, TA1535, TA98, TA1537 and *Escherichia coli* WP2uvrA.

2-Ethylhexyl methacrylate did not induce structural chromosome aberrations or polyploidy in CHL/IU cells, with or without an exogenous metabolic activation system.

SUMMARIZED DATA FROM THE STUDIES

1. Single Dose Oral Toxicity¹⁾

Purity : 99.4 %
Test species/strain : Rat/Crj:CD(SD)IGS
Test method : OECD Test Guideline 401
Route : Oral (gavage)
Doses : 0 (vehicle), 500, 1000, 2000 mg/kg/day
Number of animals/group : Males, 5; females, 5
Vehicle : Corn oil
GLP : Yes

Test results:

No deaths occurred in any group.

Based on the above results, the LD₅₀ value of 2-ethylhexyl methacrylate was concluded to be more than 2000 mg/kg for both sexes.

2. Repeat Dose and Reproductive/Developmental Toxicity¹⁾

Purity : 99.4 %
Test species/strain : Rat/Crj:CD(SD)IGS
Test method : OECD Combined Repeat Dose and Reproductive/
Developmental Toxicity Screening Test
Route : Oral (gavage)
Dosage : 0 (vehicle), 30, 100, 300, 1000 mg/kg/day
Number of animals/group : Males, 12; females, 12
Vehicle : Corn oil
Administration period : Males, 49 days
Females, from 14 days before mating to day 3 of lactation
Terminal kill : Males, day 50
Females, day 4 of lactation
GLP : Yes

Test results:

<Repeat Dose Toxicity>

For the males, the absolute kidney weights and the relative pituitary, liver and kidney weights were increased in the 300 and 1000 mg/kg groups. Suppression of body weight gain and decreased food consumption, RBC, hemoglobin, hematocrit, WBC and total protein, and increased GOT, GPT, A/G ratio, BUN and Cl, as well as focal necrosis in the liver and decrease of extramedullary hematopoiesis in the spleen were seen in the 1000 mg/kg group.

For the females, the relative kidney weights were increased in the 100 mg/kg or more groups. Suppression of body weight gain during the pre-mating, pregnancy and lactation

periods, decrease in food consumption during the pre-mating period, atrophy of the thymus, the increased absolute kidney, relative thyroid and liver weights, and decrease of extramedullary hematopoiesis in the spleen and focal malacia in the medulla oblongata were seen in the 1000 mg/kg group, one animal of which died.

The NOELs for repeat dose toxicity are considered to be 100 mg/kg for males, and 30 mg/kg for females.

<Reproductive/Developmental Toxicity>

With regard to reproductive/developmental toxicity, three of the seven females lost their pups in the 1000 mg/kg group. Nos. of corpora lutea and implantation scars were decreased in the 1000 mg/kg group. The NOELs for reproductive performance are considered to be 1000 mg/kg for males, and 300 mg/kg for females.

With regard to pups, decreased numbers of live pups born were seen in the 300 and 1000 mg/kg groups. Decreased birth, live birth and viability indices, and decreased body weights of both sexes on day 0 and day 4 after birth were seen in the 1000 mg/kg group. The NOEL for pup development is considered to be 100 mg/kg.

3. Genetic Toxicity

3-1. Bacterial test¹⁾

Purity	: 99.4 %
Test species/strain	: <i>Salmonella typhimurium</i> TA100, TA1535, TA98, TA1537, <i>Escherichia coli</i> WP2 <i>uvrA</i>
Test method	: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guidelines No. 471 and 472
Procedures	: Pre-incubation method
Solvent	: DMSO
Positive controls	: -S9 mix; AF-2 (TA100, TA98), Sodium azide (TA1535), ENNG (WP2 <i>uvrA</i>) and 9-Aminoacridine (TA1537) +S9 mix; 2-Aminoanthracene (all strains)
Doses	: -S9 mix; 39.1, 19.5, 9.77, 4.88, 2.44, 1.22, 0.610 $\mu\text{g}/\text{plate}$ (TA100, TA1535, TA1537); 313, 625, 1250, 2500, 5000 $\mu\text{g}/\text{plate}$ (WP2 <i>uvrA</i> , TA98) +S9 mix; 625, 313, 156, 78.1, 39.1, 19.5, 9.77 $\mu\text{g}/\text{plate}$ (TA100, TA1535, TA1537); 39.1, 78.1, 156, 313, 625, 1250, 2500 $\mu\text{g}/\text{plate}$ (WP2 <i>uvrA</i> , TA98)
S9	: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test	: 3
Number of replicates	: 2
GLP	: Yes

Test results:

This chemical did not induce gene mutations in the *S. typhimurium* and *E. coli* strains. Toxicity was observed at concentrations of 9.77 $\mu\text{g}/\text{plate}$ (TA100, TA1535 and TA1537) without metabolic activation, and 156 $\mu\text{g}/\text{plate}$ (TA100 and TA1535) and 625 $\mu\text{g}/\text{plate}$ (WP2 *uvrA*, TA98) and 313 $\mu\text{g}/\text{plate}$ (TA1537) with metabolic activation.

Genotoxic effects:

S. typhimurium TA100, TA1535, TA98, TA1537

	+	?	-
Without metabolic activation:	[]	[]	[*]
With metabolic activation:	[]	[]	[*]

E. coli WP2 *uvrA*

	+	?	-
Without metabolic activation:	[]	[]	[*]
With metabolic activation:	[]	[]	[*]

3-2. Non-bacterial *in vitro* test (chromosomal aberration test)²⁾

Purity	: 99.4 %
Type of cell used	: Chinese hamster lung (CHL/IU) cells
Test method	: Guidelines for Screening Mutagenicity/Testing of Chemicals (Japan) and OECD Guideline No. 473
Solvent	: Acetone
Positive controls	: -S9 mix, Mitomycin C +S9 mix, Benzo(a)pyrene
Doses	: -S9 mix (24 hr continuous treatment) : 0, 10, 20, 40, 80 $\mu\text{g}/\text{mL}$ -S9 mix (48 hr continuous treatment) : 0, 10, 20, 40, 80 $\mu\text{g}/\text{mL}$ -S9 mix (6 hr short-term treatment) : 0, 10, 20, 40, 80 $\mu\text{g}/\text{mL}$ +S9 mix (6 hr short-term treatment) : 0, 625, 1250, 2500, 5000 $\mu\text{g}/\text{mL}$
S9	: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test	: 2
GLP	: Yes

Test results:

This chemical did not induce structural chromosomal aberrations or polyploidy under the conditions of this experiment.

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
Without metabolic activation:	[]	[]	[*]	[]	[]	[*]
With metabolic activation:	[]	[]	[*]	[]	[]	[*]

- 1) The test was performed by Nihon Bioresearch Inc. Hashima Laboratory, 6-104 Majima, Fukuju-cho, Hashima, Gifu, 501-6251, Japan. Tel +81-58-392-6222 Fax +81-58-391-3171
- 2) The tests were performed by the Mitsubishi Chemical Safety Institute Ltd., 14 S-mayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-0255, Japan. Tel +81-479-46-2871 Fax +81-479-46-2874