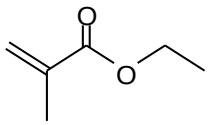
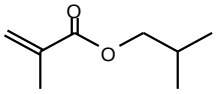
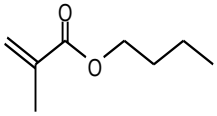
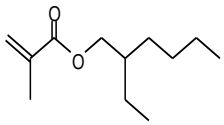
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-63-2	97-86-9	97-88-1	688-84-6
Chemical Name	Ethyl Methacrylate (EMA)	Iso-Butyl Methacrylate (i-BMA)	n-Butyl Methacrylate (n-BMA)	2-Ethylhexyl Methacrylate (2-EHMA)
Structural Formula				

SUMMARY CONCLUSIONS OF THE SIAR

Category justification

The short chain (C2-C8) unsaturated linear and branched alkyl methacrylates included in this category show Structure Activity Relationship with respect to environmental toxicity, distribution and fate, and mammalian toxicity. These esters are rapidly metabolized to methacrylic acid (CAS 79-41-4) and the structurally corresponding alcohol by non-specific carboxylesterases in several tissues. Methyl methacrylate (MMA) (CAS 80-62-6), the C_1 ester, is the largest volume methacrylate ester that has been studied extensively and reviewed in the OECD HPV Chemicals Program. As such, MMA provides a robust reference chemical for this category.

Physical-chemical properties

The physico-chemical properties of MMA, EMA, i-BMA, n-BMA and 2-EHMA are as follows: boiling point: 100.5 ºC, 118.8 ºC, 155 ºC, 163 ºC and 227.6 ºC, respectively; melting point: -48ºC, <-75ºC, -35ºC, -50ºC and $\leq$ 50ºC; vapour pressure: 42, 20, 2.1, 2.1 and 0.065 hPa at 20 ºC, respectively; Log K_{ow} at 20/25 ºC: 1.38, 1.87, 2.95, 2.99 – 3.03 and 4.95 – 5.59, respectively; and water solubility: 16 g/L (20 ºC), 4.69 g/L (20 ºC), 0.47 g/L (20 ºC), 0.36 g/L (25 ºC) and 0.0016 g/L (25 ºC), respectively.

Human Health

The members of the category are of low acute toxicity by oral, dermal and inhalation routes. Any possible trend across the category would be masked by the use of limit doses in more recent guideline studies. Median oral lethal dose values (LD_{50}) are greater than 2000 mg/kg. By inhalation the median lethal concentration is likely to be in excess of 29 mg/l (circa 5000ppm). Although acute inhalation data are not available for 2-EHMA this end-point is not considered critical due to its low vapor pressure (<1 hPa @ 20 °C). These chemicals are all typically irritating to the skin of rabbits when applied under occluded conditions and upon prolonged contact. EMA is slight to moderately irritating to the eyes whereas, i-BMA, n-BMA and 2-EHMA produce, at worst, slight irritation. All four esters appear to give equivocal results in contact sensitizing studies in guinea pigs using adjuvant. Although EMA, n-BMA and i-BMA have been reported to give positive clinical challenge responses in humans, methacrylate esters have been shown to cross-react with other methacrylates esters in both animals and humans so the possibility that the inducing agent in clinical case studies may be another methacrylate ester cannot be excluded. No cross-reactivity with acrylate esters has been reported. These data conclude that the short chain methacrylate esters are weak skin sensitizers. There are no clinical case study reports linking these esters to respiratory allergy.

In a repeat oral exposure study (OECD 422) with n-BMA the NOEL in male rats was 30 mg/kg bw/day based upon reduced splenic weights and atrophy of the splenic red pulp. The NOEL in females was 300 mg/kg bw/day based upon changes in the blood and urine parameters indicative of effects on the kidneys, however, these were not confirmed histopathologically. In a similar repeated oral exposure study (OECD 422) with EHMA, the NOAEL was 100 mg/kg bw/day in male rats and 30 mg/kg bw/day in females, based on organ weight changes in kidney (absolute and relative), without confirmatory histopathology, pituitary gland (relative), and liver (relative) in males and on organ weight changes in both liver (absolute and relative) and kidney (relative only) in females.

In a subacute inhalation study in rats with n-BMA the lead effect was the development of lesions in the olfactory region of the respiratory tract. The LOEC for this effect was 952 ppm (5626 mg/m^3) and the NOEC, 310 ppm (1832 mg/m^3). No other relevant repeat dose inhalation studies are available for other members of the category; however, extensive studies have been reported on

the inhalation toxicity of MMA, the reference chemical for this category. These studies consistently indicate that the lead effect is local degeneration of the olfactory tissue within the nasal cavity. For this effect a NOAEC of 25 ppm (104 mg/m^3) in a two-year inhalation study in rats was identified but only slight effects on the olfactory tissues have been observed at 100 ppm (416 mg/m^3). The mechanism of toxicity has been established as hydrolysis of the parent ester by tissue carboxylesterases to release methacrylic acid (MAA). Studies with MMA indicate that there is little or no progression of the effect from acute through to chronic exposures.

Recent inhalation studies, also in rats, have shown that EMA also produces olfactory lesions comparable to MMA following acute exposure at 200 ppm (948mg/m^3), but that alkyl-methacrylate esters larger than EMA do not elicit a toxic response at this dose level, mainly because their physicochemical characteristics prevent significant local uptake of the vapors (Jones, 2002). Based upon the available data a clear trend exists across the short-chain alkyl methacrylate category such that the NOAEC/LOAEC for olfactory nasal lesions increases with increasing ester size.

The NOAEC for olfactory lesions with EMA is, therefore, likely to be comparable to, or slightly higher than, that for MMA, i.e. 25 ppm (119 mg/m^3). In the case of i-BMA, the NOAEC is likely to be comparable to that found for n-BMA, i.e. 310 ppm (1832 mg/m^3). Considering the low vapor pressure of EHMA and that the saturated vapor concentration at equilibrium would only be 99 ppm (814 mg/m^3), it is unlikely that EHMA will cause nasal lesions under normal conditions of use. The methacrylate esters have been tested in vitro and in vivo for gene mutations, chromosome mutations and aneugenic effects over relevant dose ranges. There is no indication that the methacrylate esters in the category cause gene mutations.

Although there are no carcinogenicity studies available for any member of the category there is no relevant concern on carcinogenicity for MMA in humans and animals. Epidemiology data on increased tumor rates in MMA exposed cohorts are of limited reliability and cannot be related to MMA as the solely causal agent. On the basis of the analogy with MMA and the common, rapid metabolism and clearance of these esters from the body it is unlikely that they will represent a carcinogenic risk.

Some evidence of reproductive toxicity was demonstrated in one-generation rat reproductive toxicity studies conducted by OECD Guideline 422 with n-BMA and 2-EHMA. In the study of n-BMA, the number of corpora lutea and implantation sites was decreased at the 1000 mg/kg/day level giving a NOEL of 300 mg/kg/day. Similarly, in the study of 2-EHMA, the gestational period was prolonged and there was a decrease in the number of corpora lutea and implantation sites at the 1000 mg/kg/day level giving a NOEL of 300 mg/kg/day. In a dominant lethal study with short-term exposure to MMA, no effects on male fertility in mice were observed when animals had been exposed to up to 9000 ppm for a period of 5 days before mating.

High inhalation exposures to n-BMA and EMA in rats induced developmental toxicity characterized by reduced fetal body weight, but produced no embryolethality or teratogenicity even at concentrations producing overt maternal toxicity. Likewise, MMA does not cause developmental effects in rats even at inhalation exposure levels that produce maternal toxicity. With oral exposures, some evidence of developmental toxicity with n-BMA or EHMA was shown by the OECD Guideline 422 screening study (i.e. decreased number of neonates on Day 0 of lactation, decreases in parturition and live birth indices and total number of offspring in the 1000 mg/kg/day dose group), however, protocol limitations in this screen would suggest more weight be applied to definitive teratology studies. In studies of the metabolites of the butyl methacrylates (methacrylic acid and the corresponding alcohol), no effects on development were observed following oral exposure to rats and rabbits with isobutanol or by inhalation to iso-, or tertiary-butanol. Although n-butanol did produce increased rudimentary cervical ribs at 8000 ppm (about 50x the TWA), it occurred only in the presence of maternal toxicity. It is unlikely that exposure to butyl methacrylate esters with subsequent hydrolysis to methacrylic acid and the corresponding alcohol would produce blood levels of the alcohol high enough to result in developmental toxicity. Although no data are available on the parent ester i-BMA one would anticipate that by analogy with n-BMA, EMA, EHMA, and MMA, this chemical would not pose a developmental toxicity hazard.

A dose-related response was observed with EMA in the Morris Water Maze suggestive of potential for neurotoxicity. However, the clinical observations are more consistent with general systemic toxicity rather than a specific neurotoxic effect and the reviewing pathologists considered the reported spinal cord vacuolation to be artifact and the lesions reported in peripheral nerve and brain not to be treatment-related.

Environment

Model calculations indicate that the esters will be rapidly photolyzed in the atmosphere under the influence of atmospheric OH▪ radicals. They are stable under acidic and neutral conditions and hydrolyze rapidly at pH 9 and above. Based on Mackay Level III calculation, short-chain methacrylate esters will predominantly partition into the air, with the smaller esters below 2-EHMA will have a significant presence in the water phase. While EMA, i-BMA, and n-BMA do not have a significant presence in soil or sediments, EHMA has a potential to partition into soil sediments when released to the aquatic environment. All esters of the category are readily biodegradable. Based on the Log K_{ow} values of the short chain methacrylate esters the potential for

bioaccumulation is for MMA, EMA, i-BMA and n-BMA. In a bioconcentration test with fish, 2-EHMA showed a low bioconcentration factor of 37. Elimination from the aquatic compartment is expected to be rapid, evaporation and biodegradation being the main processes involved.

The esters are of low to high toxicity to aquatic organisms as toxicity increases with increasing lipophilicity and molecular size across the category with EMA being the least toxic and 2-EHMA the most toxic. This trend was consistent between all three trophic levels studied (algae, daphnia and fish) as was the general level of toxicity. The acute fish toxicity (96h LC_{50}) ranges from 100 mg/L (EMA) to 2.78 mg/L (2-EHMA). Similarly, acute invertebrate toxicity (48h EC_{50}) ranges from >66 mg/L for EMA to 4.6 mg/L for 2-EHMA and, acute algal toxicity (72h EC_{50}) ranges from >110 mg/L for EMA to 7.68 mg/L for 2-EHMA. This general trend was also observed in the long-term and chronic aquatic tests. No chronic fish studies were available for any member of the category. Chronic aquatic invertebrate data (21-day) range from a NOEC of 18 mg/L (EMA) to 0.105 mg/L (2-EHMA). Chronic algae studies (72-hour) range from a NOEC of 110 mg/L (EMA) to 5.8 mg/L (i-BMA). All data that are considered reliable for chronic aquatic toxicity support the trend of increasing toxicity with increasing molecular weight and lipophilicity.

Exposure

EMA, i-BMA, n-BMA and 2-EHMA are used by industry to make polymers. Polymers based upon EMA are used to make automotive coatings, nail sculpturing, inks and dental products; polymers based on i-BMA/n-BMA are used the manufacture of automotive coatings, lacquers and enamels, adhesives, oil additives (lubricants), emulsions for textile, leather and paper refinishing and dental products; polymers based upon n-BMA are also used in the manufacture of toners, architectural paints, , powder coatings and floor polishes; polymers based on 2-EHMA are used in lubricants, automotive coatings, paints, printing ink, additive agents, adhesives, leather, paper, lacquer and textile industries. Estimated Global production is EMA (10 kt/y); n-BMA (100 kt/y); i-BMA (10 kt/y) and 2-EHMA (2.5 kt/y) (based upon US figures, comparable production in Europe and an estimated production of 1.7kt/y 2-EHMA in Japan). N-BMA/i-BMA may be released into the environment in fugitive and stack emissions or in wastewater during its production and use in the manufacture of resins and polymers. Estimated releases into the environment from monomer and polymer production in the EU are < 0.3 t/yr n-BMA and < 0.15 t/yr i-BMA to air; < 0.15 t/yr n-BMA and < 0.05 t/yr i-BMA to water and none to soil. For n-BMA/i-BMA processing (polymerization) limited available data indicate losses of 15 g/t monomer to air and 10 g/t monomer to water. The potential for exposure to workers occupationally involved in the production of these monomers and in the subsequent manufacture and use of polymers made from these monomers is low. These monomers are used almost exclusively in the production of polymers for use by industry or consumers. Since end-use consumer products contain only trace levels of esters (as a result of polymerization), consumer exposure to methacrylate monomers is likely to be extremely low. Small quantities of EMA, and to a lesser extent i-BMA, are used in the manufacture and repair of artificial nails. Published data on occupational exposure in nail salons indicates that inhalation exposures can occur but typical levels are relatively low and below current exposure limits. The potential for dermal exposure in this use scenario cannot be excluded. Methacrylate monomers are also used in the manufacture of polymer-based dentures and prosthetics by trained dental technicians. Levels of residual monomers in these devices are controlled under an ISO standard; hence exposure via the oral mucosa will be very low.

RECOMMENDATIONS AND NATURE OF FURTHER WORK RECOMMENDED

Health: These chemicals possess properties indicating a hazard for human health (skin sensitization, skin and eye irritation). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore these chemicals are currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The category members possess properties indicating a hazard for the environment (acute toxicity between 1 and 100 mg/L). However, the chemicals in this category are of low priority for further work because of their rapid biodegradation and their limited potential for bioaccumulation