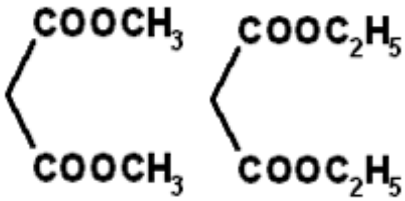
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	108-59-8, 105-53-3
Chemical Names	Category of malonic acid diesters: Dimethylmalonate (DMM) and Diethylmalonate (DEM)
Structural Formulas	

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The production and use pattern of Diethylmalonate (DEM) and Dimethylmalonate (DMM) are comparable. The two chemicals have very similar physico-chemical properties and both esters are hydrolyzed via a two step reaction to malonic acid and the corresponding alcohol, methanol or ethanol. It is likely that unspecific esterases in the body catalyze the hydrolysis. The alcohols and malonic acid are physiological substances that are metabolized via physiological pathways. Ethanol (CAS No. 64-17-5) and methanol (CAS No. 67-56-1) were assessed at SIAM 19. For ethanol it was concluded that the chemical is currently of low priority for further work, because the hazardous properties of ethanol are manifest only at doses associated with consumption of alcoholic beverages. As it is impossible to reach these exposure levels as a consequence of the manufacture and use of malonates, it can be expected that malonic acid will be the metabolite that determines the toxicity of DEM. For methanol, SIAM 19 decided that this chemical is a candidate for further work. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). The effects of methanol on the CNS and retina in humans only occur at doses at which formate accumulates due to a rate-limiting conversion to carbon dioxide. In primates, formate accumulation was observed at methanol doses greater than 500 mg/kg bw (which would require a DMM dose of more than 1000 mg/kg bw). As there were no indications of a methanol associated toxicity from a well performed repeated dose toxicity study with DMM in rodents (which are, however, known to be less sensitive to methanol toxicity than humans), and because methanol toxicity would not be expected up to doses as high as 1000 mg DMM/kg bw/day, it was concluded that methanol does not make a relevant contribution to the toxicity profile of DMM. A possible mode of action for systemic toxicity of DMM and DEM can only be deduced from the repeated dose study with DMM, indicating a reversible liver hypertrophy at the cellular level at high doses of 1000 mg/kg bw/day. This effect can be an indication of an induction of metabolism in the liver rather than a clear systemic toxicity.

Human Health

From the physical chemical properties of both substances it can be assumed that they are readily absorbed through mucous membranes and distributed into the water compartments. Absorption through skin in *in vitro* experiments in different species varied widely depending on the experimental conditions. *In vivo* skin absorption of undiluted [2-^{14}C]-DEM was highest in nude mice with 15 % absorption and lowest in pigs (2.5 %). In human skin grafted on nude mice and in hairless dogs absorption was 4 %. These experiments indicate relatively low skin absorption under non-occluded conditions. Both DMM and DEM are likely to be metabolized by esterases under cleavage of one or

two ester bonds yielding the corresponding alcohols and malonic acid monoesters or malonic acid.

No acute inhalation study is available for DMM. In the dermal toxicity study in rats following OECD guideline TG 402 and GLP (limit test) the LD50 was > 2000 mg/kg bw. An acute oral toxicity study in rats revealed an LD_{50} > 2000 mg/kg bw. In both studies no test substance related effects were observed.

For DEM only limited literature data are available. No toxicity was observed after 8 h inhalation of concentrated vapors in rats. The dermal LD_{50} in rabbits was reported to be > 16 960 mg/kg bw, the oral LD_{50} in rats 15 794 mg/kg bw. Taken together the studies for both substances suggest that they are of low acute toxicity via the oral and dermal route and likely to be also of low toxicity after inhalation exposure.

DMM was not irritating to rabbit skin in a guideline study according to OECD TG 404 and GLP. For DEM no guideline study is available on skin irritation, but a slightly irritating effect was reported in the literature after 24 hours of occlusive exposure. Both substances showed slight to moderate eye irritating effects in rabbits that were completely reversible within the observation period. The studies were conducted according or similar to OECD TG 405 and under GLP.

DMM did not reveal any skin sensitizing effect in a Bühler test according to OECD TG 406 and GLP. Reports of maximization tests in human volunteers with both, DMM and DEM did not indicate any skin sensitizing properties.
One repeated dose study in rats by the oral route (gavage) according to OECD TG 422 and GLP is available for DMM. The only effect observed was a reversible hepatocellular hypertrophy in animals of the high dose group (1000 mg/kg bw/day). The NOAEL was 300 mg/kg bw per day. Only a limited dietary 90 day study in rats is available with DEM, which indicated no treatment related effect at dose levels of 36 and 41 mg/kg bw per day for male and female animals, respectively (only one dose level was tested). Although the information available for DEM is limited, it is considered sufficient because DEM is not likely to be more toxic than DMM. Overall, the toxicity of DMM and DEM after repeated dosing is considered to be low.

Both DMM and DEM were not mutagenic in the standard Ames assay in bacteria with and without metabolic activation. DMM did not show any clastogenic activity in the *in vitro* cytogenetic assay with peripheral human lymphocytes in the presence and absence of a metabolic activation system. All tests were conducted according to OECD or EC guidelines and GLP. For both substances, there is no structural alert for genotoxicity. In conclusion, from the available information there is no indication of a mutagenic potential of the substances, both for gene mutations and chromosomal aberrations.

Based on the findings in a combined oral (gavage) repeated dose reproduction/developmental toxicity study in rats according to OECD TG 422 and GLP with DMM a NOAEL for parental toxicity of 300 mg/kg bw/day for males and females and a NOAEL for reproductive and developmental toxicity of 1000 mg/kg bw/day, the highest dose tested, can be derived. No reproductive/developmental toxicity study was available for DEM. Because it is impossible to reach blood levels of ethanol which are associated with reproductive/developmental toxicity as a consequence of the manufacture and normal use of DEM, it can be expected that malonic acid will be the metabolite that determines the toxicity of DEM. Taking also into account that DEM is not likely to be more toxic than DMM, which has shown no potential for reproductive and developmental toxicity, it is overall concluded that there is no indication for a relevant reproductive and/or developmental toxicity of DMM and DEM.

Environment

Both, dimethyl- and diethylmalonate are colorless organic liquids with an ester like odor. DMM has a melting point of –62 °C, a boiling point of 181.4 °C, a water solubility of about 142 g/l at 20 °C, a vapor pressure of 0.48 - 0.5 hPa at 20 °C and a measured log Kow of -0.05. DEM has a melting point of –48.7 to –51.1 °C, a boiling point of 199.3 °C, a water solubility of 20 g/l at 20 °C, a vapor pressure of 0.36 hPa at 25 °C and a measured log Kow of 0.96. Both substances are readily biodegradable (100 % (DMM) and 98 % (DEM) in a DOC-die away test) and undergo a two-step hydrolytic degradation in a first step to the monoester and in a second step to malonic acid and the corresponding alcohol, methanol or ethanol respectively. The half lives were shortest at pH 9, < 2.4 h (50 °C) for

both substances, and increased to 5.7 h (50 °C) and 15.9 h (50 °C) for DMM and DEM respectively at pH 7 and 859 h (50 °C) for DMM at pH 4. At pH 4 and 50 °C DEM showed less than 10 % degradation within 5 days. For photodegradation via oxidation by OH-radicals half lives of about 31 days for DMM and 4.7 days for DEM in air were estimated. For DEM a 100% photolytic ozonisation after 40 min under UV-irradiation in water was reported. The generic fugacity model I indicates that both substances are preferably distributed in the water phase (98 % for DMM and 90 % for DEM) with a low amount distributing potentially into air (1.5 and 9.9 % respectively). The fugacity model III however, indicates that a considerable amount may be distributed to the soil if the substances are primarily released into air (36 % for DMM and DEM) or soil (38 % for DMM and 44.5 % for DEM). The measured octanol-water partition coefficients (log Kow -0.05 for DMM and 0.96 for DEM) indicate a low potential for bio- or geoaccumulation.

Acute toxicity data for 3 trophic levels of the aquatic environment are available for both substances.

Acute toxicity in mg/l:

	DMM	DEM
LC_{50} fish: 96 h, *Danio rerio*	21	-
LC_{50} fish: 96 h, *Pimephales promelas*	-	12 - 17
EC_{50} Daphnia: 48 h, *Daphnia magna*	> 728	179
Algae EC_{50}: 72h, *Desmodesmus subspicatus;* growth rate (biomass)	240(92)	> 667(424)

Based on the lowest LC_{50}-value for fish of 21 mg/l for DMM and 12 mg/l for DEM and an assessment factor of 1000 PNEC-values of 21 and 12 µg/l can be derived for DMM and DEM, respectively.

No growth inhibition of DEM to terrestrial plants in soil was observed up to concentrations of > 100 mg/kg soil and no toxicity to *Eisenia fetida* was observed at concentrations of DEM of 1000 mg/kg bw after 14 days of exposure.

Exposure

The worldwide production capacity of malonates with DMM and DEM as the most important products was estimated to be more than 20 000 t/a. The breakdown by country in 2000 was estimated as follows: Europe: 8000 t/a (Sponsor country: 8000 t/a by 1 Producer), Japan 4000 t/a, China 12 000 t/a, Korea 2000 t/a, and India 600 t/a. DMM and DEM are widely used in the chemical industry as intermediates for the synthesis of a variety of organic chemicals, for example to introduce an acetic moiety or a hydroxyester group into molecules. The end products of the different processes in which malonates are used as intermediates include pharmaceuticals, agrochemicals, vitamins, fragrances and dyes. It was estimated that about one third each of the volume of DMM is used in the production of agrochemicals, pharmaceuticals and industrial chemicals. For DEM the estimated breakdown is 30 % as an intermediate for the production of agrochemicals, 50 % pharma-intermediate, 20 % as intermediate for industrial chemicals. Because of the predominant production and use in chemical industry under controlled conditions, environmental exposure from production and use is considered low. DMM is a naturally occurring substance and has been detected in a number of fruits as a volatile aroma compound for example in pineapples, bananas and blackberries.

In production from the process description very low occupational exposure is anticipated. No data are available for the uses. As the majority of the products are used as intermediates in the chemical industry a controlled exposure situation is anticipated.

With regard to consumer exposure WHO (2000) evaluated the combined daily intake of 47 flavoring substances including DEM in Europe and the US. The annual production volume of these 47 substances was 200 metric tons in Europe and 1700 metric tons in the US. From this an estimate per capita daily intake of 28 mg in Europe and 300 mg in the US was derived. This intake was considered of no concern.

DMM is contained in the Swedish and Swiss Product Registers, but not in the SPIN Database. DEM is contained in the Swedish and Swiss Product Registers and in the SPIN Database.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals of this category are currently of low priority for further work due to their low hazard profile.

Environment: The chemicals of this category possess properties indicating a hazard for the environment. Although these hazards do not warrant further work (as they are related to acute toxicity which may become evident only at high exposure levels) they should nevertheless be noted by chemical safety professionals and users. The chemicals are currently of low priority for further work.