

[FOREWORD](#)

[INTRODUCTION](#)

MALEIC ACID, DIBUTYLESTER
CAS N°: 105-76-0

SIDS INITIAL ASSESSMENT PROFILE

CAS NO	105-76-0
CHEMICAL NAME	Maleic acid, dibutylester
STRUCTURAL FORMULA	CH-COO-CH ₂ -CH ₂ -CH ₂ -CH ₃ " CH-COO-CH ₂ -CH ₂ -CH ₂ -CH ₃
<u>RECOMMENDATION OF THE SPONSOR COUNTRY</u>	
<input checked="" type="checkbox"/> presently of low concern <input type="checkbox"/> needs further work <input type="checkbox"/> candidate for in-depth review a view to possible risk reduction activities	
<u>SHORT SUMMARY OF THE REASONS WHICH SUPPORT THE RECOMMENDATION</u>	
<p>Environment:</p> <p>Maleic acid, dibutylester (DBM) is mainly used as inner softening agent for watery dispersions of co-polymers with vinylacetate. This is done in a closed system. The log Pow indicates considerable bioaccumulation potential. DBM is toxic to fish, shows influences to Daphnia and growth inhibition of algae. DBM is inherently biodegradable.</p> <p>Possible losses by spilling are very low. Calculating the (worst case) current exposure situation using PEC/PNEC shows that DBM is of little concern for the aquatic environment.</p>	
<p>Health:</p> <p>The substance shows no acute oral and inhalation toxicity but slight eye irritation and a strong skin sensitising effect were observed. The in vivo micronucleus test showed that there are no mutagenic effects.</p> <p>The substance is of low concern of human health but protective clothing and glasses are required at work places where direct skin and eye contact is possible.</p>	

FULL SIDS SUMMARY

CAS NO: 105-76-0		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL DATA				
2.1	Melting Point			< -60°C
2.2	Boiling Point			277-280°C at 988 hPa
2.3	Density			994 kg/m ³
2.4	Vapour Pressure			< 1x10 ⁻² hPa at 20°C
2.5	Partition Coefficient (log Pow)			3,38 at 20°C
2.6 A.	Water Solubility			0,173 g/l at 20°C
B.	pH-Value pKa-Value			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAYS				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG111	pH 1,2/37°C/144 h: 15% hydrolyzed pH 7,0/25°C: T _{1/2} = 2870 h pH 9,0/25°C: T _{1/2} = 50 h
3.2	Monitoring Data			
3.3	Transport and Distribution		Calculated (Fugacity Level 1 type)	
3.5	Biodegradation		(local exposure) 84/449/EWGC3	readily biodegradable
ECOTOXICOLOGICAL DATA				
4.1	Acute/Prolonged Toxicity to Fish	rainbow trout	OECD TG203	LC ₅₀ (96 hr) = 1,2 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates <i>Daphnia</i>	<i>Daphnia magna</i>	OECD TG202	EC ₅₀ (48 hr) = 21 mg/l EC ₀ =10 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Scenedesmus subspicatus</i>	OECD TG201	EC ₅₀ (72 hr) = 6,2 mg/l NOEC=4,2 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (<i>Daphnia</i>)			
4.6.1	Toxicity to Soil Dwelling Organisms			
4.6.2	Toxicity to Terrestrial Plants			
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			

FULL SIDS SUMMARY
PART 2

CAS NO: 105-76-0		SPECIES	PROTOCOL	RESULTS
TOXICITY				
5.1.1	Acute Oral Toxicity	rat, Carw.-Wi.	H.F. Smith	LD ₅₀ = 3730 mg/kg
5.1.2	Acute Inhalation Toxicity	rat, S.D.	OECD TG403	LC ₅₀ > 5 mg/l/4 hr
5.1.3	Acute Dermal Toxicity	rat, S.D.	OECD TG402	LD ₅₀ > 2000 mg/kg
5.4	Repeated Dose Toxicity	rat, Clr.	OECD-draft	NOEL = 95 mg/kg
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	S. typhi.	OECD TG471 (Ames-Test)	with met. act.= – without met. act.= –
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)			
5.6	Genetic Toxicity In Vivo	mouse	OECD TG474	genotoxic effects= –
5.8	Toxicity to Reproduction	rat, Clr.	OECD-draft	NOEL = 95 mg/kg
5.9	Developmental Toxicity/ Teratogenicity			
5.11	Experience with Human Exposure			dermatitis after occupational exposure

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

Skin irritation rat
Hyperemia disappeared after 6-9 hours

Eye irritation rabbit
Hyperemia disappeared after 24 hours

Skin sensitisation guinea pig
strong sensitising effect

SIDS INITIAL ASSESSMENT REPORT

CAS No. 105-76-0

CHEMICAL NAME Maleic acid, dibutylester

STRUCTURAL FORMULA

$$\begin{array}{c} \text{CH-COO-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3 \\ \parallel \\ \text{CH-COO-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3 \end{array}$$

General Information

Dibutylmaleinate (DBM) is a colourless fluid (melting point -60°C , boiling point $277\text{-}280^\circ\text{C}$). It has a low vapour pressure ($< 10^{-2}$ hPa) and low solubility in water (max 173 mg/l) ¹. The partition coefficient octanol/water is $\log P_{\text{OW}} 3,38$.

DBM is manufactured at a limited number of production sites in Western Europe (10.000-17.000 t/year). Production in Austria is reported to have ended by 1995. In Austria DBM is exclusively used as a chemical intermediate to produce co-polymers with vinylacetate. The co-polymers contain maximally 200 ppm free DBM (200 ppm = detection limit). The co-polymers are used in watery dispersions. Previous uses as softeners, glues, detergents etc. to our knowledge have been abandoned. Canada reported that DBM is also used as a fragrance or flavouring agent. No further information about such a use was reported ².

Environment

Environmental exposure: Possible losses by spilling are estimated to be 7 kg/year in Austria. The annual discharge into the air is estimated to be maximally 280 kg in Austria.

DBM decomposes in water at neutral pH only slowly (T_{1/2} 4 months). It degrades more rapidly at acid ³. From the 2 studies available it can be concluded that DBM is readily biodegradable ^{4, 5}. The relatively high partition coefficient octanol/water indicates considerable bioaccumulation potential. Bioaccumulation factors calculated by USES V 1.0 NL are as follows: BCF fish 111,6 l/kg, BCF worm 29 kg/kg, PEC data have been calculated by means of default values of the TGD for two German producers and were found to be 0,2 g/l and 1,2 g/l.

Effects: DBM was found to be toxic to fish (rainbow trout, *Oncorhynchus mykiss*), and a LC₅₀/96 h = 1,2 mg/l was calculated ⁶. Since this LC₅₀ calculation was based on nominal concentrations used in the fish test while actual concentrations decreased to 35% the LC₅₀ was also estimated on the basis of the geometric mean of nominal and final concentrations. From this a LC₅₀ of 0,6 mg/l was obtained. With *Daphnia magna* an

EC₅₀/24 h of 45 mg/l was found ⁷. Growth inhibition of algae (*Scenedesmus subspicatus*) was obtained with an EC₅₀ (72 h) of 6,2 mg/l ⁸.

In conclusion, DBM is discharged into air and water at low levels. The lowest LC₅₀ value is 1,2 mg/l for fish or, if based on actual concentration, 0,6 mg/l, respectively. This gives a PNEC of 12 or 1,2 g/l (or 0,6 g/l), depending on the safety factor used, namely 100 or 1000. Therefore, the PEC of 1,2 g/l which is calculated on a worst case assumption is of the same order or smaller than the PNEC. Given the current exposure situation for the two German producers DBM is of little concern for the aquatic environment.

Biodegradability

Dibutylmaleinate was tested for ready biodegradability in an OECD-screening-test according to guideline EG 84/449/EWG C.3 in September 1985. Two tests were performed in parallel. An inoculum was obtained from effluent of a waste water treatment plant. Test compound concentration in the test was DOC 20 mg/l. With Dibutylmaleinate DOC de-creases were as follows: at 5 days 35 and 13%, mean 24%, at 14 days 93 and 92%, mean 93%, at 19 days 94 and 96%, mean 95%. Thus, at least 70% were degraded within the 10-day-window. It was concluded that the test compound is readily biodegradable.

Bioaccumulation

Bioaccumulation data were calculated using the USES V 1.0 NL program. The following results were obtained:

BCF fish 111,6 l/kg
BCF worm 28,97 kg/kg
BCF stem plant 0,1937 kg/kg
BCF root plant 0,6238 kg/kg
BCF air plant 44,78 m³/kg
BCF meat 6,026 x 10⁻⁵ d/kg
BCF milk 1,905 x 10⁻⁵ d/kg

Toxicity to fish

Dibutylmaleinate was tested according to OECD guideline 203 - April 4, 1984. Six groups of 10 rainbow trouts per group were exposed for 96 hours to 0, 1.0, 1.7, 3.0, 5.2 and 9.0 mg dibutylmaleinate/l water. After 48 hours the concentration of the substance had de-creased to 33%. Concentrations were re-adjusted to 100% at this time; they decreased again to approximately 35% at termination of the study. For calculation of LC₅₀ nominal concentrations were used. In this respect the study did not conform to OECD guideline 203 according to which the concentration of the test substance should be at least 80% of the nominal concentration throughout the test. Behavioral changes of the animals (darker colour, then alterations of coordination of movements during swimming) were seen in the two highest dose groups already 5 hours after the start of beginning of exposure and later in all groups. At 48 hours 6 of 10 fish were dead at 1,7 mg/l and 0 of 10 fish at 1 mg/l. Only in the lowest exposure group (1.0 mg/l) 7 of 10 animals survived until 96 hours. The LC₅₀ was graphically determined to be 1.2 mg/l nominal concentration). Based on geometric means of

nominal and actual concentrations LC₅₀ estimates at 48 hours were approx. 0,9 mg/l and at 96 hours approx. 0,6 mg/l

Toxicity to daphnids

The acute toxicity of Maleic acid dibutylester was determined in the fresh-water crusta-cean *Daphnia magna* over a test period of 48 hours (static test) according to OECD guidelines 202 - February 1994. Concentrations of the test substance were 10, 18, 32, 56 and 100 mg/l. 20 *Daphnia* were used for each concentration and for one negative control group. To check the reliability of the test conditions potassium dichromate was used as reference substance (five concentrations between 0,2 and 3,5 mg/l, 20 *Daphnia* per concentration). Investigations performed: pH, temperature, dissolved oxygen concentration, actual test substance concentrations; number of immobile *Daphnia* after 24 and 48 hours.

No control *Daphnia* were immobilised or trapped at the surface of the water over the test period.

The EC₅₀/48h of potassium dichromate was 0,84 mg/l (95% confidence limits: 0,71 and 0,99 mg/l).

The pH of the test substance solutions was comparable to the pH of the dilution water (7,8) at the start and at the end of the test. The actual concentrations of the test substance in dilution water were about 95% and 91% of the initial concentrations after 24 resp. 48 hours in the samples measured. EC data were calculated on the basis of nominal concentrations.

Toxicity to algae

The effect of dibutylmaleinate on growth of the fresh water green algae *Scenedesmus subspicatus* was studied according to OECD guideline 201, June 7, 1984. The test was performed on exponentially growing cultures of the algae; cell numbers were counted at the start of incubation and then after 22, 46 and 71 hours in the range finding test or after 24, 48 and 72 hours in the main test. The test system was validated by negative and positive controls, potassium dichromate served as positive control. In concentrations between 0,1 mg/l and 1,5 mg/l it produced a dose dependent inhibition of algae growth with an EC₅₀ value of 0,5 mg/l. In the range finding test concentrations of dibutylmaleinate were between 0,64 mg/l and 156 mg/l, in the main test between 0,4 mg/l and 12,8 mg/l. Concentrations at the end of the incubation period were tested by HPLC. At lower concentrations recovery decreased down to 43,43%. Since the recovery in the stock solution was 96,12%, it was concluded that the low recovery at lower concentrations was caused by adsorption of dibutylmaleinate to the glass wall of the incubation vessels. Attempts to determine test compound concentrations by UV-photometry were not satisfactory. Therefore the data on inhibition of the algae growth were calculated using the nominal concentrations. The results of the study show a dose dependent inhibition of algae growth which was greater 95% after 12,8 mg/l. The EC₅₀ was estimated in the range finding test to occur approximately at 6,0 mg/l. In the main test an EC₅₀ of 6,2 mg/l was found. The No-Observed-Effect-Concentration was 4,2 mg/l.

Human Health

Human exposure: Synthesis and co-polymerisation occur in closed systems, therefore little exposure is expected at working places in production plants. The co-polymer endproduct contains free DBM at levels below 200 ppm. Exposure of workers and consumers in rooms where DBM containing dispersions are used are calculated to be maximally 10 ppb in air. Exposure modeling by means of USES V 1.0 NL revealed a total

human intake via in-direct exposure of 0,011 mg/kg daily. No information was provided on possible exposure when DBM is used as fragrance or flavor.

Health effects: Acute toxicity testing in rats revealed no evidence of toxicity by any route (oral LD₅₀ 3730 mg/kg⁹, inhal. LC₅₀ > 5000 mg/m³¹⁰, derm. LD₅₀ > 2000 mg/kg¹¹). Slight skin and eye irritation was reported in an older study from Russia¹². DBM exhibited a strong sensitizing effect on guinea pig skin¹³. Also in humans occupationally exposed to glues containing DBM a strong sensitizing effect and development of contact dermatitis was reported. In one study 10/20 exposed workers were reported to have developed contact der-matitis¹⁴

In a combined repeat dose and reproductive/developmental toxicity screening test renal tubular lesions and increased liver and kidney weights were observed in high dose animals (300 mg/kg). No adverse effect on reproductive performance was found. The NOEL was 95 mg/kg¹⁵. DBM was not found to be mutagenic in Salmonella bacteria¹⁶ and did not induce micronucleus formation in mouse bone marrow in vivo¹⁷. Therefore, according to currently known use patterns estimated human doses seem to be several orders of magnitude lower than any toxic doses noted so far in experimental animals. Protective clothing and safety goggles are required at working places where direct skin and eye contact is possible.

Acute oral toxicity

Single dose oral toxicity for rats was estimated by intubation of dosages in a logarithmic series to groups of five male rats. The animals were Carworth-Wistar rats, raised in a own colony, fed Rockland rat diet complete, weighing 90 to 120 g and not fasted before dosing. Fourteen days after dosing, mortality was considered complete. The most probable LD₅₀ value and its fiducial range were estimated by the method of W.R. Thompson (Use of Moving Averages and Interpolation to Median-Effective Dose, Bact. Rev. 11:115, 1947) using the tables of C.S. Weil (Tables for Convenient Calculation of Median-Effective Dose and Instructions in Their Use, Biometrics 8:249, 1952)

Acute inhalation toxicity

The test was performed according to OECD guideline 403 - May 12, 1981 (limit test). 5 male and 5 female Sprague-Dawley (Him:OFA) rats were exposed to an aerosol of dibutyl-maleinate by inhalation for 4 hours at a concentration of 5000 mg/m³ air in a nose-only inha-lation device. All animals survived until 4 days p.a. No substance related observations were made during and after the treatment period. At necropsy changes were noted on the lungs of 4 males and 3 females which were denoted as "small haemorrhages" apparently on the basis of macroscopic appearance. It was concluded that the inhalation LC₅₀ for male and female rats is beyond 5000 mg/m³ air.

Acute dermal toxicity

Dibutylmaleinate was tested according to OECD guideline 402 - February 24 1987 (limit test). Groups of 5 male and 5 female Sprague-Dawley (Him:OFA) rats were treated once with 2000 mg/kg body weight. Pure compound was spread on an hair-clipped area of approximately 30 cm² (corresponding to at least 10% of th body surface). All animals sur-vived until 14 days p.a. Low to medium grade erythema was noted in all

males and in 3 females one and two days p.a. In addition chromodacryorrhoea was seen in 4 males and 5 females between a few minutes and 6 hours p.a. which was considered to indicate reduced well-being of the animals caused by the dressing. No other effects were observed that could be related to treatment. Macroscopic inspection at sacrifice 14 days p.a. did not reveal overt lesions; a single occurrence of large thyroids was not assumed to be substance related. It was concluded that the LC₅₀ (dermal) of dibutylmaleinate is beyond 2000 mg/kg b.w. in male and female rats.

Skin Irritation

0,05 ml Dibutylmaleinate were daily applied to a shaved area of 8 - 9 cm² on the loin of rats during 30 days. The same area on the other side of the animals was the control area. The effect was negative, only a slight peeling was observed. 0,02-0,03 ml Dibutylmaleinate were applied to the skin on the inner side of the forearm of man. After 13 - 15 minutes they felt a slight burning and prickling. The test area was red. After 30 - 60 minutes the red-ness covered an area of 15 - 20 cm², at this time the burning and prickling disappeared. The Hyperemia disappeared after 6 - 9 hours.

Eye Irritation

Dibutylmaleinate was applied to the mucous membrane of the eyes of rabbits. 1 - 2 minutes after application the animals were rubbing the eyes. The eyelids were closed for 10 - 15 minutes. After 1 hour all animals had a slight hyperemia of the conjunctiva. The hyper-emia disappeared after 24 hours.

Skin sensitisation

The testing procedure was similar to OECD guideline 406 - May 12, 1981; the method followed was the "maximization test" of Magnusson-Kligman. GLP regulations were not applied. Female albino guinea pigs (age not indicated, body weight 340- 346 g) were used. Ten control and 20 experimental animals received 6 intracutaneous injections into a 4 x 6 cm hair- clipped skin area. 2 x 0,1 ml Freund's complete adjuvant, 2 x 0,1 ml of a 10% solution of dibutylmaleinate in corn oil, and 2 x 0,1 ml of 10% solution of dibutylmaleinate in corn oil with Freund's complete adjuvant were injected all at different locations. Controls received corn oil instead of test compound. One week later the area of injections was hair-clipped again and covered by a 2 x 4 cm filter paper with 0,3 ml of pure test compound ("Patch-Test"). Controls received a patch with corn oil. Two weeks later a filter paper patch (2 x 2 cm) containing 0,2 ml of pure test substance was placed on the hair-clipped left flank of both treated and control animals for 24 hours. 24 hours after removal of the patch 80% of the animals showed erythema (usually grade 1 to 2), after 48 hours 70% showed erythema. None of the control animals exhibited a response. It was concluded that dibutylmaleinate showed a strong sensitizing effect on guinea pig skin.

Bacterial test

Dibutylmaleinate was tested for mutagenic activity with *S.typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100. Test performance and reporting was not according to OECD guidelines and GLP regulations. Doses of test compound were 10, 50, 250, 1000 and 5000 g/plate, with and without metabolic activation using an S 9 mix from phenobarbital treated male rats. 1000 and 5000 g/plate resulted in bacterial

toxicity. Tests were performed in duplicate using adequate positive and negative controls. However, in the test with S 9 mix Endoxan (cyclophosphamide) used as the only positive control showed a positive effect only with strain TA 100 and apparently killed all other strains. Therefore the validity of the test system can not be considered sufficiently demonstrated. The test compound did not produce significant increases in mutation rates with any strain, with and without S 9 mix. Conclusion: dibutylmaleinate was not mutagenic in the present test.

Bacterial test

Dibutylmaleinate was tested for mutagenic activity with *Salmonella typhimurium* strains TA 97a, TA 98, TA 100 and TA 1535 according to OECD guideline 471 in compliance with GLP rules. Concentrations of test compounds ranged between 6 and 500 µg/plate. It is reported that 500 µg/plate were toxic. All tests were performed in the absence and presence of metabolic activation system (S9 mix from rats treated with aroclor 1240). Adequate positive and negative controls were performed and showed the reliability of the test system. The test substance did not produce, at any concentration, a significant increase of mutation frequency. It is concluded that dibutylmaleinate does not exert mutagenic activity under the conditions of the test performed.

Non-bacterial test in vivo

The test was performed according to OECD guideline 474 - May 1983. 2000 mg dibutylmaleinate per kg b.w. were administered once by gavage to 3 groups of 5 male and 5 female NMRI mice each. This dose had been selected on the basis of a range finding study but had not exhibited signs of toxicity as suggested by guideline 474 for dose selection. Animals were killed 24, 48 and 72 hours p.a. A single dose of 40 mg/kg cyclophosphamide 24 hours before sacrifice was used as positive control and clearly increased the number of micronucleated erythrocytes. The test compound did not change the ratio of polychromatic erythrocytes to all erythrocytes. At all 3 time points slight increases in the number of micro-nucleated erythrocytes were obtained which were, however, not statistically significant. The results at 24 and 48 hours were also slightly in excess of the upper limits of historical control data. In conclusion dibutylmaleinate was considered to be not mutagenic in the micronucleus test at the dose of 2000mg/kg, but a slight clastogenic effect could not be excluded.

Subacute and reproductive toxicity

This study was performed as a screening test to evaluate both (subacute and reproductive toxicity) in general and adverse effects on reproductive performance associated with repeated administration of dibutylmaleinate. The test substance was applied orally per gavage to 3 groups of 12 male and 12 female Wistar rats each, once a day. An equally sized negative control group was treated with the vehicle. The test substance was administered freshly dissolved in arachis oil at a dose volume of 5 ml per kg body weight. Doses of 0 (control), 30 (low dose), 95 (mid dose) and 300 mg (high dose) test substance per kg body weight and day were used (Dose range finding study with doses of 0, 100, 316, and 1000 mg/kg). Mating was performed on an 1:1 base after 2 weeks of pre-mating period. Couples were separated after successful mating resp. at the end of a 10-days mating period. Dams were allowed to litter normally and were sacrificed together with their offspring on day 4 of lactation. All males were necropsied together with the first dams. Dosing of both sexes was started at beginning of pre-mating period and continued until termination of the study.

Investigations performed:

Parental animals: Observation in life; body weight; feed consumption; mating results; time of parturition; hematology and clinical chemistry in males; necropsy; organ weight analyses, histopathology of selected tissues.

Offspring: Observation in life, litter weight, number, sex and viability, necropsy.

Observations in life revealed some unspecific signs of reduced well-being in both sexes and a higher incidence of dermal hyperaemia in males, altogether in the high dosed group only. Body weights of high dosed males were significantly lower than those of the controls towards the end of the dosing period. Clinical chemistry revealed significantly higher albumin, total protein and bilirubin in the high dosed males. A significant decrease in high dosed animals MCH (mean corpuscular haemoglobin) was found at haematological examination. Most prominent alterations at post mortem examination were renal tubular lesions in the high dosed males, i.e. tubular epithelial basophilia, tubular dilatation, tubular epithelial proliferation and karyomegaly. Organ weight determination revealed increased absolute and/or relative liver and kidney weights in high dosed animals of both sexes. Individual effects were noted in a single female, suffering from different lesions (heart, kidney, liver) and losing its whole litter due to lacking nursing behaviour. As this was single case, though being a high dosed animal, these effects cannot be related to the test substance without doubt. All but one fertility parameter remained without significant differences or dose relationships. The only exception was the number of dead pups at birth, which was significantly higher in both mid and high dosed groups. As all but one infant deaths in the high dosed group were in the litter of the one severely affected dam mentioned above, those deaths cannot be attributed to an adverse effect on fertility of the test substance. Therefore both significance and dose relationship are doubted. A possible sex difference in the response to the test substance cannot be proven, as both sexes have undergone different examinations.

The No-Effect-Level in this study was 95 mg Dibutylmaleinate per kg body weight and day for both sexes, defined by the mid dose of this study, where no toxic effect could be elucidated. Main target organs were liver and kidney. No adverse effect on reproductive performance could be found.

Conclusions

The only known major concern with DBM for human health is a strong sensitizing effect after direct skin contact. Therefore protective clothing and safety goggles are required at work places where direct contact to DBM is possible. For current use patterns the main route of human exposure is by inhalation, though at very low levels. Estimated exposures are several orders of magnitude lower than doses causing acute or subacute toxicity in experimental animals. Therefore the compound is regarded of low concern for human health.

References:

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- 2 Prof. Dr. K. Lederer, Institut für Chemie der Kunststoffe, Montanuniversität, A-8700 Leoben; Altstoffstudie über Di-n-butylmaleinat (April 1991)
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German producers

- Environment Canada, Ottawa, Ontario K1A 0H3, letter of July 4, 1996
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- 15 Österreichisches Forschungszentrum Seibersdorf A-2444 Seibersdorf (April 1993)
- 16 Hüls AG, D-4370 Marl, Ps-Biologie/Toxikologie, Dr. P. Schöberl, report no. 88/186 (9.5.1988)
- Österreichisches Forschungszentrum Seibersdorf A-2444 Seibersdorf (November 1993)
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SIDS INITIAL ASSESSMENT REPORT**Full SIDS Dossier****1. Chemical Identity**

CAS-number	105-76-0
Name	Maleic acid, dibutylester
Common Synonyms	Dibutylmaleinate
Empirical formula	C ₁₂ H ₂₀ O ₄
Structural formula	CH-COO-CH ₂ -CH ₂ -CH ₂ -CH ₃ " CH-COO-CH ₂ -CH ₂ -CH ₂ -CH ₃
Degree of purity (percentage by weight)	98 - 99 % w/w
Identity of major impurities	Di-n-butylfumarat, n-Butanol

2. Physical-Chemical Data**Melting or Decomposition Point**

melting point < -60°C
decomposition > 250°C

GLP: YES []
NO [X]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Boiling Point 277 - 280°C at 98,8 kPa

GLP: YES []
NO [X]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Vapour pressure < 1 x 10⁻³ kPa at 20°C

GLP: YES []
NO [X]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Partition coefficient n-Octanol/water

log Pow = 3,38 at 20°C

Method: calculated]
 measured]

GLP: YES]
 NO]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Water solubility 173 mg/l at 20°C

GLP: YES]
 NO]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Flash point (liquids) 140°C

Method: DIN 51758

GLP: YES]
 NO]

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989

Auto ignition 280°C

Method: DIN 51794

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989
 H&S-Data-Sheet February 1990

Explosion limit lower: 0,56 vol%
 upper: 3,40 vol%

Reference: Hüls AG, D-4370 Marl, Grunddatensatz April 1989
 H&S-Data-Sheet February 1990

3. Source of exposure

Production levels expressed as tons per annum

3000 tons/year (1991)

Information concerning Uses

Dibutylmaleinate is mainly used as an intermediate (Austria 200-300 tonnes/year-1991, Europe-west 10.000-17.000 tons/year). Two German producers are known, production and processing amounts are confidential. The compound is used as inner softening agent for waterdispersions of copolymers with vinylacetate, the concentration of free dibutylmaleinate in the in the co-polymers is assessed to be below 200 ppm. (200 ppm is the detection limit).

Use categories in Austria are intermediates, building material agents and surface treatment agents. The compound is not known to be marketed to the general consumer.

In Canada DBM is not produced but is imported between 100 to 1000 t/a; its use is primarily as a monomer, but also as fragrance or flavouring agent.

Human exposure: synthesis and co-polymerisation in closed systems, therefore little or no exposure at working places in production plants.

Exposure of workers and consumers in rooms where dibutylmaleinate-containing dispersions are used are calculated to be maximally 10 ppb in air (saturation concentration).

Environmental exposure: possible losses by spilling are estimated to be 7 kg/year in Austria. The annual discharge into air is estimated to be maximally 280 kg in Austria.

Exposure data and PEC estimates have been calculated for the two known German producers by the Umweltbundesamt Berlin.

German producer No. 1: production and processing amounts are confidential. No data about emission into the surface water are available. A PEC was calculated on the basis of the production and processing amount using the default values of the TGD.

The following assumptions can be made:

emission factor for production: 0,3%
emission factor for processing: 0,7%
duration of production and processing: 300 d/y
elimination in the wwtp according to the model SIMPLETREAT: 92% (log Pow: 3,38; H: 1,3 Pa.m³.mol⁻¹, readily biodegradable fulfilling the 10-day-window criterion) site specific flow rate of the receiving river for site 1. With this data a PEC of 1,2 g/l could be calculated.

German producer No. 2: production and processing amounts are confidential. The producer estimated an emission into the waste water of 1,2 t/a during production and processing. As the basis for this estimation was not clear the PEC was calculated both on the basis of estimated emission and on the basis of the production and the processing amount using the default values of the TGD.

a; PEC calculation on the basis of the estimated emission into the waste water of 1,2 t/a

The following assumptions can be made:

duration of production and processing: 300 d/y
elimination in the wwtp: 92%
site-specific flow rate of the receiving river for site 2.

With this data a PEC of 0,2 g/l was calculated

b; PEC calculation using the production and processing amounts and the default values of the TGD:

The following assumptions can be made:

emission factor for production: 0,3%
emission factor for processing: 0,7%
duration of production and processing: 300 d/y
elimination in wwtp: 92%
site-specific flow rate of the receiving river for site 2.

With this data a PEC of 1,2 g/l could be calculated.

For both German producers the PEC of 1,2 g/l (worst-case) is equal respectively less than the PNEC (dependent on the safety factor of the PNEC-calculation). Therefore no risk for aquatic environment is to be assumed for both producers under the current conditions of exposure.

Reference: Prof. Dr. K. Lederer, Institut für Chemie der Kunststoffe, Montanuniversität
A-8700 Leoben;

Altstoffstudie über Di-n-butylmaleinat (April 1991) Kemikalieinspektionen, National Chemicals Inspektorat, S-171 27 Solna, Sweden.;
 exposure information Ref.No. 7-111/92 Chemie Linz GmbH, A-4021 Linz,
 exposure information for SIDS initial assessment (January 1996) Umweltbundesamt
 Berlin (Gesch.Z. IV 1.2-97292-12/, July 1996) - Exposure data and PEC calculation
 for two German producers Environment Canada, Ottawa, Ontario K1A 0H3, letter
 of July 4, 1996

Options for disposal

Mode of disposal - incineration

Remarks

Reference: Chemie Linz AG, A-4021 Linz

4. Environment

Biodegradability

Test type:	aerobic
Test medium:	soil
Test method:	OECD 301 E
GLP	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
Test results:	biodegradable

Comments: Dibutylmaleinate was aerobically tested in as aqueous suspension for ready biodegradability according to OECD guideline 301 E - 12.5.1981. Two tests each in 2 independent assays were performed. An inoculum obtained from soil was incubated with dibutylmaleinate, the amount added to the test volume of 1 litre appears to have been 31,35 or 31,5 mg (=100% dissolved organic carbon, DOC). As a positive control sodium benzoate was tested and was found to be degraded to at least 95% within 28 days. Therefore the test procedure was considered valid. In one of 2 tests in each assay the decrease of DOC to below 70% took less than 28 days, in the 2 other assays more than 28 days. Over 70% degradation was reached within 10 days after the 10% degradation level was exceeded (day 35: 0/0% degradation; day 42: 32/50% degradation; day 49: 84/86% degradation). Thus, although degradation started late, the 10 day criterion appears to have been fulfilled. It may be concluded that the present study suggests ready biodegradability of DBM, including fulfilment of the 10-day-window-criterion.

Reference: Österreichisches Forschungszentrum Seibersdorf

Ges.m.b.H., A-2444 Seibersdorf (September 1991)

Biodegradability

Test type: aerobic

Test medium: effluent from waste water treatment plant

Test method: EG 84/449 EWG C.3

GLP YES []
NO [X]

Test results: ready biodegradable

Comments: Dibutylmaleinate was tested for ready biodegradability in an OECD-screening-test according to guideline EG 84/449/EWG C.3 in September 1985. Two tests were performed in parallel. An inoculum was obtained from effluent of a waste water treatment plant. Test compound concentration in the test was DOC 20 mg/l. Marlon A was used as control compound, results obtained with Marlon A are not reported. With Dibutylmaleinate DOC decreases were as follows: at 5 days 35 and 13%, mean 24%, at 14 days 93 and 92%, mean 93%, at 19 days 94 and 96%, mean 95%. Thus, at least 70% were degraded within the 10-day-window. It was concluded that the test compound is readily biodegradable.

Reference: Hls AG, Prfinstitut für Biologie, P.O.Box 1320,
D-45764 Marl, Letter of March 11,1996

Abiotic degradation

Test method: OECD 111

GLP YES [X]
NO []

Test results:

Percentage of degradation after certain period:

pH 1,2/37EC/144 hours: Dibutylmaleinate was hydrolysed to a yield of 15,0%

pH 4,0/37EC: T2: > 2 year, no significant degradation was observed

pH 7,0/25EC: T2: 2870 hours

pH 9,0/25EC: T2: 50 hours

Reference: LPT Laboratory of Pharmacology and Toxicology,
D-2104 Hamburg, report no. 7950/93 (Juli 1993)

Bioaccumulation

Bioaccumulation data were calculated using the USES V 1.0 NL program. The following results were obtained:

BCF fish 111,6 l/kg
 BCF worm 28,97 kg/kg
 BCF stem plant 0,1937 kg/kg
 BCF root plant 0,6238 kg/kg
 BCF air plant 44,78 m³/kg
 BCF meat 6,026 x 10⁻⁵ d/kg
 BCF milk 1,905 x 10⁻⁵ d/kg

5. Ecotoxicological Data

Toxicity to fish

Test species: rainbow trout

Test method: ECD 203

GLP YES
 NO

Test results: LC₅₀/96 hours: 1,2 mg/l

Comments: Dibutylmaleinate was tested according to OECD guideline 203 - April 4, 1984. Six groups of 10 rainbow trouts per group were exposed for 96 hours to 0, 1.0, 1.7, 3.0, 5.2 and 9.0 mg dibutylmaleinate/l water. After 48 hours the concentration of the substance had decreased to 33%. Concentrations were re-adjusted to 100% at this time; they decreased again to approximately 35% at termination of the study. For calculation of LC₅₀ nominal concentrations were used. In this respect the study did not conform to OECD guideline 203 according to which the concentration of the test substance should be at least 80% of the nominal concentration throughout the test. Behavioral changes of the animals (darker colour, then alterations of co-ordination of movements during swimming) were seen in the two highest dose groups already 5 hours after the start of beginning of exposure and later in all groups. At 48 hours 6 of 10 fish were dead at 1,7 mg/l and 0 of 10 fish at 1 mg/l. Only in the lowest exposure group (1.0 mg/l) 7 of 10 animals survived until 96 hours. The LC₅₀ was graphically determined to be 1.2 mg/l nominal concentration). Based on geometric means of nominal and actual concentrations LC₅₀ estimates at 48 hours were approx. 0,9 mg/l and at 96 hours approx. 0,6 mg/l.

Reference: ÖZ - Seibersdorf, A-2444 Seibersdorf (September 1991)

Toxicity to daphnids

Test species: Daphnia magna Straus (cladocera, crustaceans)

Test method: OECD 202

GLP YES
 NO

Test results: EC₅₀ /24h: 45 mg/l
 EC₅₀ /48h: 21 mg/l
 EC₀ /48h: 10 mg/l
 EC₁₀₀/48h: 32 mg/l

Method used to calculate EC₅₀: graphical

Comments: The acute toxicity of Maleic acid dibutylester was determined in the fresh-water crustacean *Daphnia magna* over a test period of 48 hours (static test) according to OECD guidelines 202 - February 1994. Concentrations of the test substance were 10, 18, 32, 56 and 100 mg/l. 20 *Daphnia* were used for each concentration and for one negative control group. To check the reliability of the test conditions potassium dichromate was used as reference substance (five concentrations between 0,2 and 3,5 mg/l, 20 *Daphnia* per concentration). Investigations performed: pH, temperature, dissolved oxygen concentration, actual test substance concentrations; number of immobile *Daphnia* after 24 and 48 hours. No control *Daphnia* were immobilised or trapped at the surface of the water over the test period.

The EC₅₀/48h of potassium dichromate was 0,84 mg/l (95% confidence limits: 0,71 and 0,99 mg/l).

The pH of the test substance solutions was comparable to the pH of the dilution water (7,8) at the start and at the end of the test. The actual concentrations of the test substance in dilution water were about 95% and 91% of the initial concentrations after 24 resp. 48 hours in the samples measured. EC data were calculated on the basis of nominal concentrations.

Reference: Österreichisches Forschungszentrum Seibersdorf
 Ges.m.b.H., A-2444 Seibersdorf (Februar 1994)

Toxicity to algae

Test species: *Scenedesmus subspicatus*

Test method: OECD 201

GLP YES
 NO

Test results: EC₅₀ (72 hours) 6,2 mg/l
 NOEC 4,2 mg/l

Comments: The effect of dibutylmaleinate on growth of the fresh water green algae *Scenedesmus subspicatus* was studied according to OECD guideline 201, June 7, 1984. The test was performed on exponentially growing cultures of the algae; cell numbers were counted at the start of incubation and then after 22, 46 and 71 hours in the range finding test or after 24, 48 and 72 hours in the main test. The

test system was validated by negative and positive controls, potassium dichromate served as positive control. In concentrations between 0,1 mg/l and 1,5 mg/l it produced a dose dependent inhibition of algae growth with an EC₅₀ value of 0,5 mg/l. In the range finding test concentrations of dibutylmaleinate were between 0,64 mg/l and 156 mg/l, in the main test between 0,4 mg/l and 12,8 mg/l. Concentrations at the end of the incubation period were tested by HPLC. At lower concentrations recovery decreased down to 43,43%. Since the recovery in the stock solution was 96,12%, it was concluded that the low recovery at lower concentrations was caused by adsorption of dibutylmaleinate to the glass wall of the incubation vessels. Attempts to determine test compound concentrations by UV-photometry were not satisfactory. Therefore the data on inhibition of the algae growth were calculated using the nominal concentrations. The results of the study show a dose dependent inhibition of algae growth which was greater 95% after 12,8 mg/l. The EC₅₀ was estimated in the range finding test to occur approximately at 6,0 mg/l. In the main test an EC₅₀ of 6,2 mg/l was found. The No-Observed-Effect-Concentration was 4,2 mg/l.

Reference: Agrolinz Ges.m.b.H. A-4060 Leonding, Report No. 1137,
Project No. M9204 (14.7.1992)

6. Toxicological Data

Acute oral toxicity

Test species/strain: rat, Carworth-Wistar

Test method: range finding test

GLP YES []
NO [X]

Test results: LD₅₀ 3730 mg/kg

Comments: Single dose oral toxicity for rats was estimated by intubation of dosages in a logarithmic series to groups of five male rats. The animals were Carworth-Wistar rats, raised in a own colony, fed Rockland rat diet complete, weighing 90 to 120 g and not fasted before dosing. Fourteen days after dosing, mortality was considered complete. The most probable LD₅₀ value and its fiducial range were estimated by the method of W.R. Thompson (Use of Moving Averages and Interpolation to Median-Effective Dose, Bact. Rev. 11:115, 1947) using the tables of C.S. Weil (Tables for Convenient Calculation of Median-Effective Dose and Instructions in Their Use, Biometrics 8:249, 1952)

Reference: H.F. Smith, C.P. Carpenter, C.S. Weil, U.C. Pozzani, Range-Finding Toxicity
Data, Archives of Industrial Hygiene and Occupational Medicine, volume 10,
page 61-68, 1954

Acute inhalation toxicity

Test species/strain: rat, Him:OFA, Sprague Dawley, SPF

Test method: OECD 403

GLP YES
NO

Test results: LC₅₀ >5000 mg/m³

Comments: The test was performed according to OECD guideline 403 - May 12, 1981 (limit test). 5 male and 5 female Sprague-Dawley (Him:OFA) rats were exposed to an aerosol of dibutylmaleinate by inhalation for 4 hours at a concentration of 5000 mg/m³ air in a nose-only inhalation device. All animals survived until 4 days p.a. No substance related observations were made during and after the treatment period. At necropsy changes were noted on the lungs of 4 males and 3 females which were denoted as "small haemorrhages" apparently on the basis of macroscopic appearance. It was concluded that the inhalation LC₅₀ for male and female rats is beyond 5000 mg/m³ air.

Reference: Österreichisches Forschungszentrum Seibersdorf,
A-2444 Seibersdorf (Juli 1992)

Acute dermal toxicity

Test species/strain: rat, Him:OFA, Sprague Dawley, SPF

Test method: OECD 402

GLP YES
NO

Test results: LD₅₀ >2000 mg/kg

Comments: Dibutylmaleinate was tested according to OECD guideline 402 - February 24 1987 (limit test). Groups of 5 male and 5 female Sprague-Dawley (Him:OFA) rats were treated once with 2000 mg/kg body weight. Pure compound was spread on an hair-clipped area of approximately 30 cm² (corresponding to at least 10% of the body surface). All animals survived until 14 days p.a. Low to medium grade erythema was noted in all males and in 3 females one and two days p.a. In addition chromodacryorrhoea was seen in 4 males and 5 females between a few minutes and 6 hours p.a. which was considered to indicate reduced well-being of the animals caused by the dressing. No other effects were observed that could be related to treatment. Macroscopic inspection at sacrifice 14 days p.a. did not reveal overt lesions; a single occurrence of large thyroids was not assumed to be substance related. It was concluded that the LC₅₀ (dermal) of dibutylmaleinate is beyond 2000 mg/kg b.w. in male and female rats.

Reference: Österreichisches Forschungszentrum Seibersdorf,

 A-2444 Seibersdorf (Müz 1992)
Skin Irritation

Test species/strain: rat, man

GLP YES []
 NO [X]

Comments: 0,05 ml Dibutylmaleinate were daily applicated to a shaved area of 8 - 9 cm² on the loin of rats during 30 days. The same area on the other side of the animals was the control area. The effect was negative, only a slight peeling was observed. 0,02-0,03 ml Dibutylmaleinate were applicated to the skin on the inner side of the forearm of man. After 13 - 15 minutes they felt a slight burning and prickling. The test area was red. After 30 - 60 minutes the redness covered an area of 15 - 20 cm², at this time the burning and prickling disappeared. The Hyperemia disappeared after 6 - 9 hours.

Reference: I.G. Gadalina, W.A.Druzhinina, T.A. Kochetkova, Study of the skin-irritating and sensitizing action of dibutyl maleate and polydibutyl maleate plasticizers, Gig. Aspekty Okhr. Okruzhayushchei Sredy, page 37-42, 1976.

Eye Irritation

Test species/strain: rabbit

GLP YES []
 NO [X]

Comments: Dibutylmaleinate was applicated to the mucous membrane of the eyes of rabbits. 1 - 2 minutes after application the animals were rubbing the eyes. The eyelids were closed for 10 - 15 minutes. After 1 hour all animals had a slight hyperemia of the conjunctiva. The hyperemia disappeared after 24 hours.

Reference: I.G. Gadalina, W.A. Druzhinina, T.A. Kochetkova, Stydy of the skin-irritating and sensitizing action of dibutyl maleate and polydibutyl maleate plasticizers, Gig. Aspekty Okhr. Okruzhayushchei Sredy, page 37-42, 1976.

Skin sensitisation

Test species/strain: Albino guinea pig, Bor:DHPW

Test method: Maximization test - Magnusson, Kligman

GLP YES []
 NO [X]

Test results: strong sensitizing effect

Number of animals with skin reaction at challenge: 80%(24 hours)

Number of animals with skin reaction in control group at challenge: 0%

Comments: The testing procedure was similar to OECD guideline 406 - May 12, 1981; the method followed was the "maximization test" of Magnusson-Kligman. GLP regulations were not applied. Female albino guinea pigs (age not indicated, body weight 340- 346 g) were used. Ten control and 20 experimental animals received 6 intracutaneous injections into a 4 x 6 cm hair- clipped skin area. 2 x 0,1 ml Freund's complete adjuvant, 2 x 0,1 ml of a 10% solution of dibutylmaleinate in corn oil, and 2 x 0,1 ml of 10% solution of dibutylmaleinate in corn oil with Freund's complete adjuvant were injected all at different locations. Controls received corn oil instead of test compound. One week later the area of injections was hair-clipped again and covered by a 2 x 4 cm filter paper with 0,3 ml of pure test compound ("Patch-Test"). Controls received a patch with corn oil. Two weeks later a filter paper patch (2 x 2 cm) containing 0,2 ml of pure test substance was placed on the hair-clipped left flank of both treated and control animals for 24 hours. 24 hours after removal of the patch 80% of the animals showed erythema (usually grade 1 to 2), after 48 hours 70% showed erythema. None of the control animals exhibited a response. It was concluded that dibutylmaleinate showed a strong sensitising effect on guinea pig skin.

Reference: Hls AG, D-4370 Marl, WL Produktsicherheit, Toxikologie, Bericht No. 1011 (22.7.1987)

Repeated dose toxicity

Test species/strain: rat, CRL:(WI)BR

Test method: Draft of OECE-Guideline: "Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test"; March 12, 1990

GLP YES [X]
NO []

Test results: see reproductive toxicity - page 16

Bacterial test

Test species/strain: Salmonella typhimurium/TA 1535, TA 1537, TA 1538, TA 98, TA 100

Test method: B.N. Ames, J.Mc. Cann, E. Yamasahi, Mutation Research, 31 6, 347-364 (1975)

GLP YES
NO

Test results: Minimum concentration of test substance at which toxicity to bacteria was observed:
with metabolic activation: 1000 g/plate
without metabolic activation: 1000 g/plate
Concentration of the test compound resulting in precipitation:
5000 g/plate

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comments: Dibutylmaleinate was tested for mutagenic activity with *S.typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100. Test performance and reporting was not according to OECD guidelines and GLP regulations. Doses of test compound were 10, 50, 250, 1000 and 5000 g/plate, with and without metabolic activation using an S 9 mix from phenobarbital treated male rats. 1000 and 5000 g/plate resulted in bacterial toxicity. Tests were performed in duplicate using adequate positive and negative controls. However, in the test with S 9 mix Endoxan (cyclophosphamide) used as the only positive control showed a positive effect only with strain TA 100 and apparently killed all other strains. Therefore the validity of the test system can not be considered sufficiently demonstrated. The test compound did not produce significant increases in mutation rates with any strain, with and without S 9 mix. Conclusion: dibutylmaleinate was not mutagenic in the present test.

Reference: Hls AG, D-4370 Marl, Ps-Biologie/Toxikologie,
Dr. P. Schberl, report no. 88/186 (9.5.1988)

Bacterial test

Test species/strain: *Salmonella typhimurium*/TA 97a, TA 98, TA 100, TA 1535A

Test method: OECD 471 (with the updating made by the OECD Consultation Meeting of Experts on Genetic Toxicity test Methods, Nov./Dec. 1992)

GLP YES
NO

Test results: Minimum concentration of test substance at which toxicity to bacteria was observed:
with metabolic activation: 500 g/plate
without metabolic activation: 500 g/plate
Concentration of the test compound resulting in precipitation:
5000 g/plate

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comments: Dibutylmaleinate was tested for mutagenic activity with Salmonella typhimurium strains TA 97a, TA 98, TA 100 and TA 1535 according to OECD guideline 471 in compliance with GLP rules. Concentrations of test compounds ranged between 6 and 500 µg/plate. It is reported that 500 µg/plate were toxic. All tests were performed in the absence and presence of metabolic activation system (S9 mix from rats treated with aroclor 1240). Adequate positive and negative controls were performed and showed the reliability of the test system. The test substance did not produce, at any concentration, a significant increase of mutation frequency. It is concluded that dibutylmaleinate does not exert mutagenic activity under the conditions of the test performed.

Reference: Österreichisches Forschungszentrum Seibersdorf
A-2444 Seibersdorf (November 1993)

Non-bacterial test in vivo

Test species/strain: mouse, Crl:NMRI BR

Test method: OECD 474

GLP: YES
NO

Effect on Mitotic Index or P/N Ratio: 1,60/1,57

Genotoxic effects:	+	?	-
	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comments: The test was performed according to OECD guideline 474 - May 1983. 2000 mg dibutylmaleinate per kg b.w. were administered once by gavage to 3 groups of 5 male and 5 female NMRI mice each. This dose had been selected on the basis of a range finding study but had not exhibited signs of toxicity as suggested by guideline 474 for dose selection. Animals were killed 24, 48 and 72 hours p.a. A single dose of 40 mg/kg cyclophosphamide 24 hours before sacrifice was used as positive control and clearly increased the number of micronucleated erythrocytes. The test compound did not change the ratio of polychromatic erythrocytes to all erythrocytes. At all 3 time points slight increases in the number of micronucleated erythrocytes were obtained which were, however, not statistically significant. The results at 24 and 48 hours were also slightly in excess of the upper limits of historical control data. In conclusion dibutylmaleinate was considered to be not mutagenic in the micronucleus test at the dose of 2000mg/kg, but a slight clastogenic effect could not be excluded.

Reference: Österreichisches Forschungszentrum Seibersdorf Ges.m.b.H. A-2444

Seibersdorf (Mai 1992)

Reproductive toxicity

Test species/strain: rat, CRL:(WI)BR

Test method: Draft of OECD-Guideline: "Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test"; March 12, 1990

GLP: YES
NO

Test results: NOEL for P generation 95 mg/kg
NOEL for F1 generation
NOEL for F2 generation

Maternal and Paternal general toxicity:

Reproductive toxicity observed in parental animals (fertility, gestation, reproductive organ toxicity, etc.):
Only in high dosed animals (300 mg/kg): body weights significantly lower, significantly higher albumin, total protein and bilirubin, renal tubular lesions, increased liver and kidney weights

Comments: This study was performed as a screening test to evaluate both (subacute and reproductive toxicity) in general and adverse effects on reproductive performance associated with repeated administration of dibutylmaleinate. The test substance was applied orally per gavage to 3 groups of 12 male and 12 female Wistar rats each, once a day. An equally sized negative control group was treated with the vehicle. The test substance was administered freshly dissolved in arachis oil at a dose volume of 5 ml per kg body weight. Doses of 0 (control), 30 (low dose), 95 (mid dose) and 300 mg (high dose) test substance per kg body weight and day were used (Dose range finding study with doses of 0, 100, 316, and 1000 mg/kg). Mating was performed on an 1:1 base after 2 weeks of pre-mating period. Couples were separated after successful mating resp. at the end of a 10-days mating period. Dams were allowed to litter normally and were sacrificed together with their offspring on day 4 of lactation. All males were necropsied together with the first dams. Dosing of both sexes was started at beginning of pre-mating period and continued until termination of the study.

Investigations performed:

Parental animals: Observation in life; body weight; feed consumption; mating results; time of parturition; hematology and clinical chemistry in males; necropsy; organ weight analyses, histopathology of selected tissues.

Offspring: Observation in life, litter weight, number, sex and viability, necropsy.

Observations in life revealed some unspecific signs of reduced well-being in both sexes and a higher incidence of dermal hyperaemia in males, altogether in the high dosed group only. Body weights of high dosed males were significantly lower than those of the controls towards the end of the dosing period. Clinical chemistry revealed significantly higher albumin, total protein and bilirubin in the high dosed males. A significant decrease in high dosed animals MCH (mean corpuscular haemoglobin) was found at haematological examination. Most prominent alterations at post mortem examination were renal

tubular lesions in the high dosed males, i.e. tubular epithelial basophila, tubular dilatation, tubular epithelial proliferation and karyomegaly. Organ weight determination revealed increased absolute and/or relative liver and kidney weights in high dosed animals of both sexes. Individual effects were noted in a single female, suffering from different lesions (heart, kidney, liver) and losing its whole litter due to lacking nursing behaviour. As this was single case, though being a high dosed animal, these effects cannot be related to the test substance without doubt. All but one fertility parameter remained without significant differences or dose relationships. The only exception was the number of dead pups at birth, which was significantly higher in both mid and high dosed groups. As all but one infant deaths in the high dosed group were in the litter of the one severely affected dam mentioned above, those deaths cannot be attributed to an adverse effect on fertility of the test substance. Therefore both significance and dose relationship are doubted. A possible sex difference in the response to the test substance cannot be proven, as both sexes have undergone different examinations.

The No-Effect-Level in this study was 95 mg Dibutylmaleinate per kg body weight and day for both sexes, defined by the mid dose of this study, where no toxic effect could be elucidated. Main target organs were liver and kidney. No adverse effect on reproductive performance could be found.

Reference: Österreichisches Forschungszentrum Seibersdorf
A-2444 Seibersdorf (April 1993)

7. Experience with human exposure

An outbreak of dermatitis occurred in an envelope making factory among workers who were packing envelopes and looking after envelope machines. Although the process was fully automated, the workers had to clean the machines and were exposed to dibutylmaleinate, which was added to a polyvinylacetate glue.

About 20 persons were working with envelope machines operating with PVA glue. In January 1983, the first worker had skin complaints and, during the following 12 years, 11 employees developed dermatitis. All affected workers except one were female. The skin lesions were usually a red, scaly or vesicular dermatitis involving the fingers, hands, and in some cases the forearms. Of 11 patients with skin complaints 10 showed a positive response in patch tests to glues containing dibutylmaleinate or to 10% dibutylmaleinate dissolved in acetone; none of the patients responded to other glues not containing dibutylmaleinate. The test with 10% dibutylmaleinate in acetone was applied to 20 controls with eczematous disorders. All were negative. The glue containing dibutylmaleinate was removed from the envelope factory and 3 months later, dermatitis had disappeared from the employees.

Reference: Thormann J., Hansen I., Misfeldt J.
Occupational dermatitis from dibutylmaleinate,
Contact Dermatitis 1985, vol 13; 314-316

8. Initial Assessment

Dibutylmaleinate (DBM) is a colourless fluid (melting point -60EC, boiling point 277-280EC). It has a low vapour pressure ($< 10^{-3}$ kPa) and low solubility in water (max 173 mg/l). The partition coefficient octanol/water is $\log P_{OW}$ 3,38.

DBM is manufactured at a limited number of production sites in Western Europe (10.000-17.000 t/year). Production in Austria is reported to be ended by 1995. In Austria DBM is exclusively used as a chemical intermediate to produce Co-polymers with vinylacetate. The co-polymers contain maximally 200 ppm free DBM (200 ppm = detection limit). The co-polymers are used in watery dispersions. Previous uses as softener, glue, detergent etc. to our knowledge have been abandoned. Canada reported that DBM is also used as a fragrance or flavouring agent.

Human Health

Human exposure: Synthesis and co-polymerisation occur in closed systems, therefore little exposure is expected at working places in production plants. The co-polymer endproduct contains free DBM at levels below 200 ppm. Exposure of workers and consumers in rooms where DBM containing dispersions are used are calculated to be maximally 10 ppb in air. Exposure modelling by means of USES V 1.0 NL revealed a total human intake via indirect exposure of 0,011 mg/kg daily. No information was provided on possible exposure when DBM is used as fragrance or flavour.

Health effects: Acute toxicity testing in rats revealed no evidence of toxicity by any route (oral LD_{50} 3730 mg/kg, inhalative $LC_{50} > 5000$ mg/m³, dermal $LD_{50} > 2000$ mg/kg). Slight skin and eye irritation was reported in an older study from Russia. DBM exhibited a strong sensitising effect on guinea pig skin. Also in humans occupationally exposed to glues containing DBM a strong sensitising effect and development of contact dermatitis was reported. In one study 10/20 exposed workers were reported to have developed contact dermatitis.

In a combined repeat dose and reproductive/developmental toxicity screening test renal tubular lesions and increased liver and kidney weights were observed in high dose animals (300 mg/kg). No adverse effect on reproductive performance was found. The NOEL was 95 mg/kg. DBM was not found to be mutagenic in Salmonella bacteria and did not induce micronucleus formation in mouse bone marrow in vivo.

Therefore, according to currently known use patterns estimated human doses seem to be several orders of magnitude lower than any toxic doses noted so far in experimental animals. Protective clothing and safety goggles are required at working places where direct skin and eye contact as possible.

Environment

Environmental exposure: Possible losses by spilling are estimated to be 7 kg/year in Austria. The annual discharge into the air is estimated to be maximally 280 kg in Austria.

DBM decomposes in water at neutral pH only slowly (T₂ is 4 months). It degrades more rapidly at acid or alkaline pH (at pH 9,0 T₂ is 50 hours). From the 2 studies available it can be concluded that DBM is

readily biodegradable. The relatively high partition coefficient octanol/water indicates considerable bioaccumulation potential. Bioaccumulation factors calculated by USES V 1.0 NL are as follows: BCF fish 111,6 l/kg, BCF worm 29 kg/kg, PEC data have been calculated by means of default values of the TGD for two German producers and were found to be 0,2 :g/l and 1,2 :g/l.

Effects: DBM was found to be toxic to fish (rainbow trout, *oncorhynchus mykiss*), and a $LC_{50}/96$ h 1,2 mg/l was calculated. Since this LC_{50} calculation was based on nominal concentrations used in the fish test while actual concentrations decreased to 35% the LC_{50} was also estimated on the basis of the geometric mean of nominal and final concentrations. From this a LC_{50} of 0,6 mg/l was obtained. With *Daphnia magna* an $EC_{50}/24$ h of 45 mg/l was found. Growth inhibition of algae (*Scenedesmus subspicatus*) was obtained with an EC_{50} (72 h) of 6,2 mg/l.

In conclusion, DBM is discharged into air and water at low levels. The lowest LC_{50} value is 1,2 mg/l for fish or, if based on actual concentration, 0,6 mg/l, respectively. This gives a PNEC of 12/1,2 :g/l (or 0,6 :g/l), depending on the safety factor used, namely 100 or 1000. Therefore, the PEC of 1,2 :g/l which is calculated on a worst case assumption is in the same order or smaller than the PNEC. Given the current exposure situation for the two German producers DBM is of little concern for the aquatic environment.

9. Conclusions

The only known major concern with DBM for human health is a strong sensitising effect after direct skin contact. Therefore protective clothing and safety goggles are required at work places where direct contact to DBM is possible. For current use patterns the main route of human exposure is by inhalation, though at very low levels. Estimated exposures are several orders of magnitude lower than doses causing acute or subacute toxicity in experimental animals. Therefore the compound is regarded of low concern for human health.

EXTRACT FROM IRPTC LEGAL FILE

File: 17.01 LEGAL

rn : 1317110

systematic name:2-Butenedioic acid(Z)-,dibutyl ester
 common name :dibutyl maleate
 reported name :DIBUTYL MALEATE
 cas no :105-76-0 rtecs no :JH4735000
 area : USA type : REG

subject	specification	descriptor
USE		RSTR
FOOD	ADDIT	RSTR
STORE		RSTR
MANUF		RSTR
PACK		RSTR

REFERS TO HOMO AND COPOLYMERS.; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF SUBSTANCES WHICH ARE CONDITIONALLY APPROVED TO BE USED AS COMPONENTS OF THE UNCOATED OR COATED FOOD CONTACT SURFACE OF PAPER AND PAPERBOARD FOR USE WITH FOODS HAVING THE PROPERTIES OF A DRY SOLID WITH NO FREE FAT OR OIL ON THE SURFACE. THESE SUBSTANCES ARE NOT TO BE USED IN QUANTITIES WHICH EXCEED THAT REQUIRED TO ACCOMPLISH THEIR INTENDED PHYSICAL OR TECHNICAL EFFECT AND ARE SO USED AS TO ACCOMPLISH NO EFFECT IN FOOD OTHER THAN THAT ORDINARILY ACCOMPLISHED BY PACKAGING.

entry date: NOV 1991 effective date: 1977

title: INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS;
 COMPONENTS OF PAPER AND PAPERBOARD IN CONTACT WITH DRY FOOD
 original : FEREAC, FEDERAL REGISTER, 42 , , 14554 , 1977
 amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 21 , 176 , 180 , 1988

File: 17.01 LEGAL

rn : 1408569

systematic name:2-Butenedioic acid(Z)-,dibutyl ester
 common name :dibutyl maleate
 reported name :MALEIC ACID, DIBUTYL ESTER
 cas no :105-76-0 rtecs no :JH4735000
 area : EEC type : REG

subject	specification	descriptor
FOOD		RQR
GOODS		MXL
GOODS		PRMT

THE SUBSTANCE IS INCLUDED IN THE LIST OF MONOMERS AND OTHER STARTING SUBSTANCES, WHICH MAY CONTINUE TO BE USED FOR THE MANUFACTURE OF PLASTICS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS UNTIL 1 JANUARY 1997 PENDING A DECISION ON THEIR INCLUSION IN THE LIST OF AUTHORIZED SUBSTANCES. THE USE OF THE SUBSTANCE IS SUBJECT TO THE RESTRICTIONS SPECIFIED THEREIN. PLASTIC MATERIALS AND ARTICLES SHALL NOT TRANSFER THEIR CONSTITUENTS TO FOODSTUFFS IN QUANTITIES EXCEEDING 10MG/DM² OF SURFACE AREA OF MATERIAL OR ARTICLE OR 60 MG/KG OF FOODSTUFFS IN THE SPECIFIED CASES. VERIFICATION OF COMPLIANCE WITH THE MIGRATION LIMITS SHALL BE CARRIED OUT IN ACCORDANCE WITH DIRECTIVES 82/711/EEC AND 85/572/EEC.

entry date: SEP 1995 effective date: 01JAN1991

title: COMMISSION DIRECTIVE OF 23 FEBRUARY 1990 RELATING TO PLASTICS MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS (90/128/EEC)

original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L75 ,
19 , 1990
amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L90 ,
,26 , 1993