SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-42-2
Chemical Name	2,2'-iminodiethanol (diethanolamine, DEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2,2'-Iminodiethanol (diethanolamine, DEA) is well absorbed following oral administration in rats (57%) and to a lower degree after dermal administration (3-16% in rats; 25 – 60% in mice). When applied dermally, DEA appears to facilitate its own absorption, as higher doses were more completely absorbed than lower doses. DEA (20 mg/cm²) applied to skin preparations *in vitro* showed penetration rates of 6.68% (mouse) > 2.81 % (rabbit) >0.56% (rat) > 0.23% (human). Distribution to the tissues was similar via all routes examined. DEA is cleared from the tissues with a half-life of approximately 6 days. The highest concentrations are observed in liver and kidney. Metabolism after oral administration revealed non-metabolized DEA and smaller proportions of N-methyl-DEA (N-MDEA), N,N-dimethyl-DEA (N'N-DMDEA) and DEA-phosphates co-eluting with phosphatidyl ethanolamine and phosphatidyl choline. After digestion, 30% of the phospholipids were identified as ceramides and the remaining 70% as phosphog1ycerides. DEA is excreted primarily in urine as the parent molecule (25-36%), with lesser amounts of O-phosphorylated and N-methylated metabolites. Accumulation of DEA at high levels in liver and kidney is assumed by a mechanism that normally conserves ethanolamine, a normal constituent of phospholipids. DEA is incorporated as the head group in phospholipids, presumably via the same enzymatic pathways that normally utilize ethanolamine.

DEA has a moderate acute oral toxicity, while it is considered low after inhalation or dermal exposure. Oral LD50 values ranged from 780 -3,540 mg/kg bw in rats, from 3,300 – 4,570 mg/kg bw for mice and were reported as 2,200 mg/kg bw for rabbits and Guinea pigs. Inhalation risk test showed no mortality in rats after an 8 h exposure to an atmosphere enriched with vapour. A dermal LD_{50} value of 13,000 mg/kg bw was reported for rabbits. DEA is a skin and severe eye irritant in rabbits and caused upper respiratory tract irritation in subchronic studies in rats. No information was available on the respiratory irritation in humans. DEA is not a skin sensitizer in animals and available information in humans suggests no such effects. A slightly higher incidence of skin sensitization in cutting fluid workers is of a secondary nature, due to conditions not attributable to DEA (wet skin, chronic solvent exposure). Nose-only exposure of rats to DEA aerosols for 3 months resulted in systemic effects such as anaemia, adaptive liver and kidney effects, damage of male reproductive organs and upper respiratory tract irritation. No functional or morphological evidence of neurotoxicity was observed. The NOAEC for systemic effects was 15 mg/m³ and the NOAEC for upper respiratory tract irritation was 3 mg/m³.

Repeated unoccluded dermal application of ethanolic DEA solutions in subacute and subchronic studies with rats and mice led to mortality at high dose levels (≥500 mg/kg bw in rats; ≥1000 mg/kg bw in mice). In rats, systemic signs of toxicity consisted predominantly of anaemia and nephropathy. In addition, liver weights were increased without a histopathological correlate. In mice, systemic effects occurred mainly in the form of liver and kidney damage. In both species, local skin irritation was observed. A NOAEL for

systemic effects or local skin irritation could not be achieved (LOAEL 32 mg/kg bw in rats; 80 mg/kg bw in mice). In rats, subchronic oral treatment via the drinking water caused mortality at the high dose in males (5000 ppm). Impaired body weight gains were observed at concentrations equal to or higher than 320 ppm in females and 630 ppm in males. Systemic effects consisted of anaemia, nephrotoxicity, cortical vacuolization of adrenal glands and demyelinization of brain/spinal cord without any neurofunctional finding. In males, damage of reproductive organs in the form of testicular degeneration and associated weight changes and impaired spermatology was observed. Based on anaemia observed, a LOAEL of 25/14 mg/kg bw (equal to 320/160 ppm) was achieved in males/females.

In the subchronic oral study in mice, mortality was observed in males at ≥5000 ppm and in females at ≥2500 ppm. Body weight gain was decreased in both species at concentrations of 1250 ppm (females) or 2500 ppm (males) and higher. Systemic effects consisted of hepato- and nephrotoxicity and myocardial degeneration. The most sensitive effect was necrotic liver damage at all concentrations. A LOAEL of 104/142 mg/kg bw (equal to 630/630 ppm) was noted in males/females.

In subacute (14 days) oral screening examinations in rats and mice, DEA revealed some immune-modulating effects at dose levels with overt signs of systemic toxicity. The most sensitive parameter was red blood cell alteration with a LOAEL of 50/100 mg/kg bw in rats and mice, respectively, based on reduced numbers of reticulocytes.

DEA did not induce reverse mutations in *Salmonella typhimurium* or *Escherichia coli* and had no effect on gene conversion in *Saccharomyces cerevisiae*. In mammalian *in vitro* systems, DEA did not induce chromosomal aberrations in rat hepatocytes, gene mutation in mouse lymphoma cells, sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells. DEA formulated in ethanol did not induce micronuclei *in vivo* in peripheral blood erythrocytes of mice after repeated unoccluded dermal application for 13 weeks at doses clearly showing systemic availability.

DEA formulated in ethanol showed no oncogenic potential in the rat after unoccluded daily dermal exposure for 2 years. In the dermal mouse carcinogenicity study using similar exposure techniques, there was an increased incidence of liver neoplasms in males and females at all doses tested and an increased incidence of renal tubule adenomas in males at the high dose level only. The liver tumours in mice were considered to be directly related to the observed increase in the cellular proliferation rate, which is due to the observed enzyme induction, weak peroxisome proliferation and choline depletion with subsequent disturbance of its metabolism. While nitrosamine formation has been highlighted as a matter of concern for DEA, and for this reason it has been banned for use in cosmetics in the EU, nitrosamine formation was ruled out under the conditions of this study. Benign kidney tumours (adenomas) were only observed in male mice at the high dose level at a low incidence, when using serial sections. Based on the increased S-phase synthesis observed in this organ, it is conceivable that a similar non-genotoxic mode of action involving choline deficiency is responsible for the renal tubular adenomas.

In short term tests on carcinogenicity, DEA was not carcinogenic, when tested in the Tg.Ac transgenic mouse model up to topical dose levels exceeding the MTD. Cell transformation in Syrian hamster embryo cells in vitro was observed predominantly in the range of cytotoxic concentrations but supplementation of choline completely inhibited this effect.

Various mechanistic *in vitro* and *in vivo* studies identified that DEA induced choline depletion is the key event in the toxic mode of action. DEA decreased gap junctional intracellular communication in primary cultured mouse and rat hepatocytes, but all these events were prevented with choline supplementation. DNA hypomethylation was observed in mouse hepatocytes as a further epigenetic mechanism involved in liver tumourigenesis.

DEA decreased phosphatidylcholine synthesis by blocking the cellular uptake of choline in vitro, but these events did not occur in the presence of excess choline.

DEA increased S-phase DNA synthesis in mouse hepatocytes but had no effect on apoptosis. No such effects were noted in human hepatocytes *in vitro*. Apparent differences in the susceptibility of two different mice strains (B6C3F1 > C57BL) were noted. B6C3F1 mice are extremely sensitive to non-genotoxic effects and are known to possess a relatively high incidence of spontaneous liver tumours.

Moreover, chronic stimulation and compensatory adaptive changes of hepatocyte hypertrophy and proliferation are able to enhance the incidence of common spontaneous liver tumours in the mouse by mechanisms not relevant to humans. Analysis of gene expressions in animal studies showed an increase in genes associated with cell proliferation, while a decrease in genetic processes relevant for apoptotic mechanisms was observed.

There was no specific reproduction toxicity and fertility study available but there was an influence on the male reproductive system at the high concentration in the 3-month inhalation study in rats. The NOAEC for male fertility parameters was 0.15 mg/l. When DEA was orally administered to rats via the drinking water for 13 weeks, decreases in testis and epididymis weights, testicular degeneration, atrophy of the seminal vesicles and prostate glands and associated effects on spermatology were observed. The NOAEL for fertility effects in males was 48 mg/kg bw. In all of these studies no histopathological effects were observed in female reproductive organs.

DEA exposure to an aerosol in a nose-only exposure system led to maternal toxicity at the highest concentration (0.2 mg/l) and induced at this dose level signs of embryo- or fetotoxicity in the form of an increased number of foetuses with skeletal variations. Malformations were not observed. The NOAEC for maternal and prenatal developmental toxicity was 0.05 mg/l.

Prenatal developmental toxicity of DEA following dermal application was investigated in rats and rabbits. In rats, maternal toxicity was substantiated by moderate to severe skin irritation, reduced maternal body weight gain, increased kidney weights and haematological effects including anaemia, abnormal red cell morphology and decreased platelet count. In the foetuses, increased incidences of skeletal variations were observed. The LOAEL for maternal toxicity was 150 mg/kg bw, while the NOAEL for prenatal developmental toxicity was 380 mg/kg bw. The NOAEL for teratogenicity was 1500 mg/kg bw. In rabbits, doses displayed marked skin irritation, reduced body weight gain and food consumption and discoloured kidneys. The NOAEL for maternal toxicity was 35 mg/kg bw, the NOAEL for prenatal developmental toxicity including teratogenicity was 350 mg/kg bw, the highest dose tested.

Orally applied DEA within a developmental toxicity study in rats caused maternal toxicity in the form of increased mortality at high dose levels. Reduced body weight/body weight gain and food consumption and increased kidney weight were observed. Developmental toxicity consisted of an increase in postimplantation mortality and early postnatal mortality as well as reduced pup body weight. The NOAEL for maternal and postnatal developmental toxicity was 50 mg/kg bw. Thus, pre- and postnatal developmental toxicity was only observed in the presence of clear maternal toxicity and at dose levels considered as high.

Environment

The colourless solid DEA is completely miscible with water at ambient temperature and has a negligible vapour pressure of 0.0028 hPa (25 °C). The measured log K_{OW} of -2.18 (25 °C) and the calculated BCF of 3.16 indicate a low potential for bioaccumulation. The Henry's law constant of 3.97 x 10-6 Pa*m3/mol (uncharged) is considered as an indication for low volatility. The calculated Koc of uncharged DEA is 1 (corrected log Koc = 0). Thus, the potential for adsorption to soil, sediment, and suspended solid may be low. However, binding of the substance to the matrix of soils (and sediments) with high capacities for cation exchange (e.g. clay) can not be excluded for the charged molecule. The measured pKa value of 8.92 (23 °C) indicates that at environmentally relevant conditions of pH 6 – 8, the molecule will predominantly occur in the charged (cationic) form. At pH values > 9, DEA will predominantly be present as the uncharged species.

According to Mackay Level I modelling, uncharged DEA will distribute almost completely into water (99.99 %). DEA is readily biodegradable according to OECD criteria. Potential for anaerobic degradation of DEA was also observed. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life of the uncharged molecule for a 12-hour day and 1.5E06 OH/cm3: 2.4 hours = 0.1 day; for a 24-h day and 0.5E06 OH/cm3: 4.2 hours = 0.2 days). At environmental pH conditions hydrolysis is not expected to be a relevant degradation process due to the absence of hydrolysable groups The lowest reliable acute toxicity values for aquatic species were as follows:

Pimephales promelas (fish)	96-h LC_{50} = 1370 mg/l (nominal)
Daphnia magna (invertebrates)	48-h EC_{50} = 55 mg/l (nominal)
Pseudokirchneriella subcapitata	96-h E_rC_{50} = 2.2 mg/l (nominal)
Pseudomonas sp. (microorganisms)	16-h TTC = 16 mg/l (nominal)

In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 0.78 mg/l (nominal, based on analytical verification).

Exposure

DEA belongs to the ethanolamines group that includes monoethanolamine (MEA), diethanolamine (DEA) and triethanolamine (TEA). Large-scale production of DEA is carried out by the reaction of ethylene oxide and excess ammonia, followed by fractionation of the three ethanolamines (mono-, di- and tri-ethanolamine).

The annual world production in 2005 for the ethanolamines was estimated at 1,510,000 tons, subdivided into 400,000 tons/a for Europe, 780,000 tons/a for North and South America, 30,000 tons/a for Middle East, and 300,000 tons/a for the Asia/Pacific region. Individual capacity data on DEA were not available.

Ethanolamines are used widely as intermediates in the production of anionic and non-ionic surfactants, which have become commercially important as detergents, textile and leather chemicals, and emulsifiers. Their uses range from drilling and cutting oils to medicinal soaps and high-quality toiletries. DEA is an important additive of corrosion inhibitors, particularly in coolants for automobile engines. DEA is also employed as an additive in lubricants and in cement/concrete production. Large amounts of DEA are used as such in closed systems for absorptive gas purification to remove weakly acidic components. In the production of detergents, cleaners, fabric softeners and metalworking fluids DEA is used for acid neutralization and to prevent soil deposition. DEA is also used as an intermediate in the production of morpholine, photographic chemicals and polyurethanes. In addition, DEA is used as a building block for agrochemicals.

The SPIN database for Substances in Preparations in Nordic Countries lists a wide variety of uses of DEA registered in Denmark (DK), Norway (N), Sweden (S), and Finland (FIN). In the most recent year reported (2004), 520 DEA-containing preparations accounting for a total volume of 19865.8 tons were registered in Denmark. In Norway, Sweden, and Finland 103 (856.8 t), 307 (459.0 t), and 75 (132.7 t) products were registered in 2004, respectively. Use categories included intermediates, cleaning/washing agents, paints, lacquers and varnishes, surface treatment, cutting fluids, pH-regulation agents, impregnation materials, surface-active agents, corrosion inhibitors, process regulators, colouring agents, reprographic agents, lubricants and additives. The use in consumer preparations was indicated for products registered in Norway and Sweden.

According to the Commission of the European Communities, general public use is known for cleaning/washing agents, disinfectants, colouring agents, construction materials additives, corrosion inhibitors, cutting oil, and others.

Some of the above mentioned applications may not be representative of, or comparable to current conditions. According to EU Council Directive 76/768 EEC, the use of DEA in cosmetics is prohibited in the European Union.

Releases of DEA into the environment may occur during manufacturing and processing in the industry.

DEA was not detected in a study carried out in 1978 in any of the 21 samples taken from surface water (limit of determination: 0.3 - 0.34 µg/l) in Japan.

DEA was detected in German surface waters of the rivers Elbe at 0.34 µg/l – 0.58 µg/l, Mulde at 2.54 µg/l - 4.6 µg/l, Neibe at 0.72 µg/l - 1.8 µg/l and Rhine at 0.30 µg/l - 0.59 µg/l.

With respect to Canada's National Pollutant Release Inventory, total on-site releases in Canada of DEA and its salts accounted for 32.6 tonnes in the reporting year 2005.

During production and internal processing at BASF AG, Ludwigshafen (Germany), less than 100 kg/a (threshold value for releases to air according to the German Emission Register) were emitted to the air in 2004. At the production site of INEOS Oxide (Lavera, France; Plaquemine, USA) the whole process is performed in a closed system. Only the vents of the distillation columns are emitting to air. The average mass loss is <0.01 kg C*x*H*y*/ton DEA produced.

Data regarding emission via waste water treatment effluent are not available from BASF AG production and processing sites. At the production site of INEOS, average production loss via the aqueous effluent resulting from the production is <0.001 ton TOC/ton DEA produced. The streams are treated in waste water treatment units.

Occupational exposure to DEA can occur during manufacture, distribution, and use. Due to the negligible vapour pressure of DEA, the potential for inhalation exposure is minimized, with dermal exposure the most likely route.

At BASF AG, Ludwigshafen site, DEA is produced in one production plant and is becoming further processed within 8 other operations and plants. During the time period between January 2001 and December 2006 an overall number of 53 workplace exposure data were collected, covering all operations by means of personal air sampling (PAS). The reported data are 8 hour shift average values (TWA). In Germany, there is no official work place exposure limit value. The DFG MAK-value is 1 mg/m^3 (as an aerosol, inhalable fraction). For the production plant the highest recorded value was 0.026 mg/m^3. At the filling stations the maximum value recorded was 0.062 mg/m^3. The overall range of the measurement results (53 data) was < 0.019 to 0.062 mg/m^3.

Direct consumer exposure to DEA is anticipated to be low based on recent use changes and regulations such as the Cosmetic Directive in Europe.

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

Human Health: The chemical is currently of low priority for further work. The chemical possesses a hazard for human health (skin/eye/respiratory irritant, repeated-dose, reproductive/developmental toxicity). Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute toxicity to green algae and *Daphnia magna*: EC_{50} between 1 and 100 mg/l). However, the chemical is of low priority for further work because of its rapid biodegradation and its limited potential for bioaccumulation.