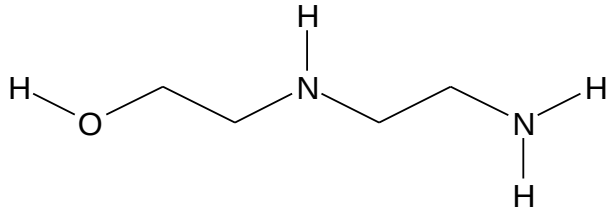
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-41-1
Chemical Name	2-(2-aminoethylamino)ethanol (AEEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Unless otherwise stated, all studies were either in compliance with, or broadly consistent with, OECD Test Guidelines (TGs). 2-(2-aminoethylamino)ethanol (AEEA) is rapidly absorbed following oral administration to female Wistar rats (t½ values 0.1-0.2 hours). Maximum blood levels were reached within 0.5 hours. Excretion was also rapid with most of the dose (85 - 98 %) recovered in the 0 - 48 hour urine, less in feces and only very low quantities in expired volatiles and as $^{14}CO_2$. The plasma elimination of orally administered ^{14}C-AEEA was biphasic, with alpha and beta elimination t½ -values of 1.6 - 1.8 hours and 16.7 - 17.3 hours, respectively. Only the parent compound AEEA was found in plasma. Most of AEEA was excreted unchanged in the urine and 2 out of 4 metabolites are of unknown structure. The pregnancy status did not cause significant differences in absorption, elimination, excretion, and metabolic profile following the oral administration of AEEA.

After dermal application of a 10-fold higher dose, no quantifiable plasma levels were reached. Urinary excretion was quantifiable, and bioavailability was approx. 10 % compared to the oral route. The organ distribution was low and comparable in all experiments, and no significant difference occurred with respect to dose level, route of exposure, pregnancy status.

The acute oral LD_{50}-value was > 2000 mg/kg bw in rats (AEEA purity >99.5 %). Symptoms of toxicity were noted in animals receiving more than 2000 mg/kg bw including dyspnoea, apathy, and staggering, and the substance caused gastric irritation following single oral dosing. The acute toxicity of AEEA was largely influenced by caustic effects as neutralized solutions of AEEA showed no toxicity at otherwise fatal concentrations. Deaths occurred within one or two days post treatment. No inhalation hazard was noted in rats exposed to saturated atmospheres for 6 or 8 hours. The acute dermal LD_{50}-value was > 2000 mg/kg bw in rats and in rabbits. Skin irritation and necroses were noted at the treated sites. AEEA was corrosive to the rabbit's skin and the rabbit's eye.

AEEA was a skin sensitizer in the Guinea Pig Maximization Test and the mouse Local Lymph Node Assay (LLNA). Cross reactions were noted in Guinea pigs induced with AEEA and challenged with Di-, Triethyleneamine, Ethylenediamine and Piperazine.

Clinical observations and positive human patch test results indicate a potential of an allergic contact dermatitis in humans. Inhalation of fumes of soldering flux and of AEEA caused delayed onset of severe allergic asthma that persisted for several hours or days in cable jointers who had been occupationally exposed to fumes of flux containing AEEA. No such reports were retrieved in the 30 years prior to 2006, which could be explained by increased industrial hygiene standards.

AEEA was tested in rats at 60, 250, and 1000 mg/kg bw/day in an oral gavage 28-day study. Blood chemistry

revealed statistically significantly increased glutamine-oxaloacetic transaminase activity only in males at the mid and high dose and decreased cholesterol in high dose females. In urine, protein was increased at 1000 mg/kg bw/day in both sexes. Urinary specific gravity was increased in mid- and high dose females, and volume was decreased in the high dose females. Increased absolute and relative kidney weights in males and increased relative kidney weight in females were observed at the high dose ($p<0.01$). Histopathologically, deposition of amphophilic bodies and swelling in the renal proximal tubules were noted in all animals at the high dose and in males at 250 mg/kg bw/day. In the stomach, thickening of the mucosa at the limiting ridge was noted in all animals at 250 and 1000 mg/kg bw/day. All effects except those in kidneys and stomach were reversible in animals allowed to recover for 14 days. The NOAEL was 60 mg/kg bw/day in both sexes.

In a 28-day dermal study, rats were dosed with 0, 100, 300 or 1000 mg/kg bw/day. No evidence of systemic toxicity was observed in the animals. The only treatment related effects observed in the study were localized skin effects at the site of test material application consistent with the known dermal irritancy/corrosivity of AEEA. The NOEL for systemic toxicity was 1000 mg/kg bw/day.

In general it may be concluded that the systemic toxicity of AEEA is low, and that the primary effect is irritancy after oral and dermal exposure. While no systemic toxicity was observed after dermal exposure, slight changes in clinical chemistry, urinalysis, and kidneys were noted after oral exposure with a high NOAEL of 250 mg/kg bw per day if the local irritation of the stomach is discounted.

There are no indications that AEEA possesses genotoxic properties. No potential for genetic toxicity of AEEA was indicated in the Ames Test (Standard-plate or Preincubation method) using *S. typhimurium* (TA98, TA100, TA1535, TA1537) with and without metabolic activation including doses that were bacteriotoxic. In the mammalian cell forward mutation assay using Chinese hamster ovary cells (CHO/HGPRT) AEEA was not genotoxic even at cytotoxic concentrations both with and without metabolic activation. This also holds for Sister Chromatid Exchanges in the same cell line. No increase of structural chromosomal changes was noted in Chinese Hamster lung cells. A slight but statistically significant increased polyploidy was noted in one experiment (48h exposure) with AEEA without metabolic activation. However, this effect was not observed in the other experiments with or without metabolic activation, and no repeat experiment was conducted to verify the finding after 48h exposure. AEEA also tested negative for induction of Unscheduled DNA Synthesis (UDS) in isolated rat hepatocytes.
In a mouse bone marrow Micronucleus Test no increased frequency of micronuclei was noted in male and female mice after oral exposure. AEEA was tested in negative in male *Drosophila melanogaster* using the Sex-Linked Recessive Lethal assay in feeding and injection experiments.

No carcinogenicity study is known to exist. As a secondary amine, AEEA can form a nitrosamine under certain conditions. Some nitrosamines are suspected to be carcinogenic.

Developmental toxicity was observed with AEEA after oral (gavage) treatment with 0, 50, 250 or 1,000 mg/kg bw per day following the OECD TG 421 screening protocol. Effects were observed in the aorta and associated major arteries such as carotids and pulmonary arteries and consisted predominantly of aneurysms at 50 and 250 mg/kg bw per day, while no pups were delivered at 1,000 mg/kg bw per day due to a lack of implants in adult females. In a follow up developmental toxicity study (OECD 414) with 0, 0.5, 2, 10 and 50 mg/kg bw per day, no such findings were obtained at 50 mg/kg bw per day, a dose level, which caused a high incidence of those findings in the OECD TG 421 study. There was no indication of maternal toxicity, embryo-/fetotoxicity in this study. Histological investigations of pups in follow up mechanistic studies revealed dissecting aneurysms and/or focal necrosis in greater vessels such as aorta, pulmonary trunk, and arteria subclavia. Fragmented elastic fibers could be shown using special staining technique. It is assumed that the damage of vessel structure is occurring in utero; however the development of aneurysms is likely to occur during and shortly after birth when arterial blood pressure is significantly increased. Follow up studies indicate that these lesions in pups are visible shortly after birth, and that aneurysms undergo repair mechanisms with scars as residual findings in pups raised up to 60 days after birth. Physiological post birth maturation of vessels and effective repair mechanism explain why no mortality was seen in rats orally dosed with 1000 mg/kg bw in the 28-day study. In this study the animals were treated after maturation of the vessel system. A follow-up study similar to OECD TG 421 (0.2, 1, 5 and 50 mg/kg bw per day) indicated a LOAEL of 0.2 mg/kg bw per day based on aneurysms observed. From the original TG 421 screening study it is unclear if the lack of implants at the high dose level of 1000 mg/kg per day was due to embryotoxicity or fertility effects (fertility index 60% in the high dose group compared to 90-100% in the others). A NOAEL of 250 mg/kg bw was established for possible fertility effects.

Environment

2-(2-aminoethylamino)ethanol (aminoethylethanolamine, AEEA) is a colorless to yellowish liquid which is completely soluble in water (25 °C / 1013 hPa). The melting point, given as pour point, is -38 °C, the boiling point is 243.1 °C, and the density is 1.024 g/cm3 at 25 °C. Following SPARC estimations, at environmentally relevant pH values (pH 7-9) the substance exists predominantly (75 – 95 %) as a cation in aqueous solution. The vapor pressure of 0.018 hPa at 25 °C was computer-modeled (EASE for Windows, v2.0) using an experimentally derived value of 0.21 hPa at 63.5 °C as input data. The measured log Pow of -1.46 (25 °C) and the measured BCF of ≤ 3.7 do not indicate a significant potential for bioaccumulation.

According to Mackay Level I, AEEA will distribute almost completely into water (99.99 %). The calculated Koc of uncharged AEEA is 3.524 (log Koc = 0.547). 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. Data on the stability of AEEA in water are not available. In a recently performed manometric respirometry test (OECD TG 301 F), AEEA was shown to be readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life: 1.1 hours).

Results on acute aquatic toxicity are available for fish (*Pimephales promelas*; LC_{50} (96 hours): 640 mg/l), invertebrates (*Daphnia magna*; EC_{50} (48 hours): 22 mg/l), and algae (*Scenedesmus subspicatus*; EbC_{50} (72 hours): 210 mg/l; ErC_{50} (72 hours): 354 mg/l). In the three tests, high pH values as determined in the highest concentrations tested might have had contributory effects on the observed toxicity. Results of toxicity tests with microorganisms revealed EC_{50} values of ≥ 135 mg/l. Based on the acute toxicity studies, AEEA is considered of moderate acute toxicity to aquatic organisms. A PNECaqua of 0.022 mg/l was obtained by applying an assessment factor of 1000 on the lowest endpoint, the result of the acute Daphnia test.

Exposure

The annual world production capacity in 2003 for ethyleneamines was estimated at 295,000 tons, subdivided into 138,000 tons/annum for Europe, 127,000 tons/annum for United States, and 30,000 tons/annum for Japan. Individual capacity data on AEEA are not available. AEEA is mostly used as an intermediate in the production of surfactants, for specialty personal care products, pharmaceuticals, and cleaning agents. Smaller volumes of AEEA are also used as chemical intermediates in the production of textile, polyurethane, lube oil, and fuel additives as well as in manufacturing of chelating agents and polyols. In Europe AEEA is also applied in production of hardeners for epoxy resins and as an additive in polyurethane (PU) production. PU and epoxy resins are often employed as building materials. In the Sponsor Country, AEEA is primarily used as a chemical intermediate for the synthesis of amphoteric surfactants (85 %) and an amide wax (15 %) for consumer uses. Minor use patterns are reported for varnishes and surface coating agents. In Switzerland the use of AEEA in soldering flux is reported for industrial products.

During processing and use of consumer products containing AEEA, exposure may occur via inhalation or skin contact. At the production sites, it is technically ensured that exposure of workers to AEEA is minimized. Significant exposure is normally not expected during production, transportation, and sampling, because these processes are largely enclosed. Occupational exposure is therefore limited to situations of maintenance and accidental spills. Concerning production and processing of AEEA, worker exposure via air is negligible. Exposure measurements resulted in concentrations that were below the limits of detection (<0.001 to 0.09 mg/m³). Consumers may be exposed through the use of waxes and surfactants (amphoteric tensides) which contain un-reacted AEEA at concentrations which are in the range of 5 pm, or below 10 ppm in final cosmetic products.

Releases of AEEA into the environment may occur during manufacturing and processing in the industry. Another source of environmental exposure may also be expected from the use of surfactants and waxes containing AEEA. AEEA is readily biodegradable and although no actual exposure information is available, only very small amounts of AEEA are to be expected in effluents of wastewater treatment plants at manufacturing and processing sites. During production and processing in 2004 at BASF AG (Ludwigshafen, Germany), AEEA was not emitted to air. Data regarding emission via waste water treatment effluent are not available from this site.

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

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (skin and eye irritation, skin sensitizer, developmental toxicity on blood vessels). Further mechanistic studies to elucidate the detailed mode of action on developing blood vessels and the relevance of this finding for man are underway. Member countries are invited to perform an exposure assessment for consumers including residues in cosmetics and workers and if necessary a risk assessment.

Environment: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute toxicity to aquatic invertebrates: EC_{50} between 10 and 100 mg/l). However the chemical is of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.