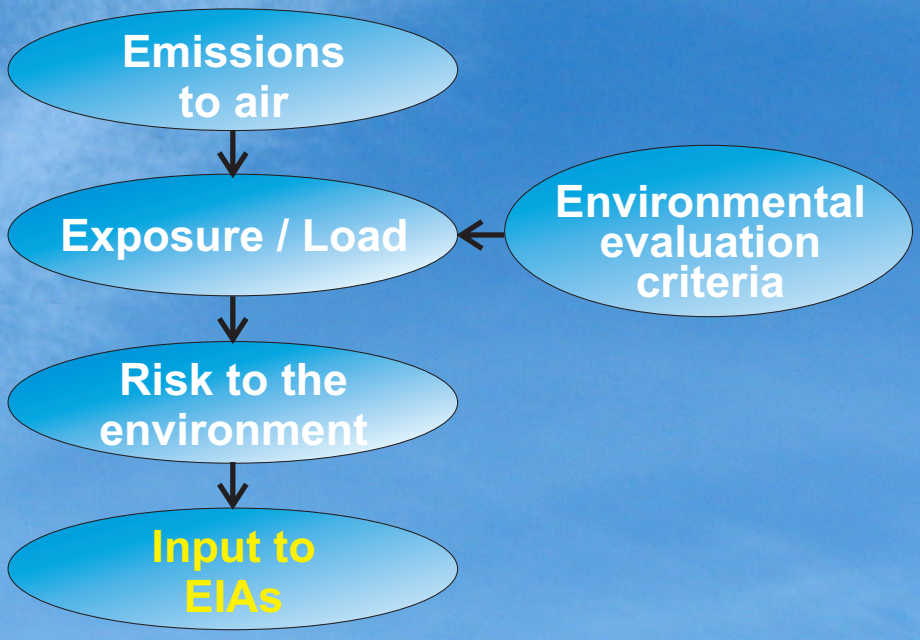
Task 7.1 Report:
Health Effects of Different Amines Relevant for CO_2 Capture

Phase I: CO_2 and Amines Screening Study for Environmental Risks



Norwegian Institute of Public Health
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Preface

CO_2 capture and storage (CCS) has been proposed for two Norwegian gas-fired power plants as a measure to reduce CO_2 emissions to the atmosphere. A leading technology for CO_2 capture is through the use of amines. The *CO_2 and Amines Screening Study Project* began with *Phase I* in May 2008. The project was initiated by the Norwegian Institute for Air Research (NILU) based on the results of an expert meeting in October 2007, and discussions with the Norwegian Pollution Control Authority (SFT). The expert meeting and the following Phase I project is based upon the concern that the emissions from CO_2 capture using amines could be potentially harmful to the environment and human health, and that the existing information regarding these subjects were quite limited, thus demanding further examination and analysis.

The project was graciously sponsored by the following:

- Gassnova SF (CLIMIT)
- Statoil Hydro ASA
- Shell Technology Norway AS

The following institutes participated in the project:

- Centre for Theoretical and Computational Chemistry (CTCC) Department of Chemistry at the University of Oslo, responsible for the theoretical study on the atmospheric degradation of selected amines (Task 3).
- The Norwegian Institute of Public Health (FHI), responsible for the effects to human health (Task 7).
- Norwegian Institute for Nature Research (NINA), responsible for the effects to terrestrial ecosystems (Task 8).
- Norwegian Institute for Water Research (NIVA), responsible for the effects on freshwater ecosystems (Task 9).
- Norwegian Institute for Air Research (NILU), responsible for project management/coordination, including the chemical screening report, models report, worst case study report, and the summary report (Task 1, 2, 4, 5, 6, and 10).

The project sponsors comprised the Steering Committee, which gave useful guidance to the project and its administration. The project sponsors function within the Steering Committee also gave them an active role in reviewing all project reports and documentation.

Contents

Summary

Monoethanolamine (MEA), piperazine, aminomethylpropanol (AMP) and methyldiethanolamine (MDEA) appear to be relevant compounds for the capture of CO_2 in gas-fired power stations. MEA and piperazine have during several years been used in various industries and consumer products and may represent a significant potential for human exposure. Therefore, a considerable number of experimental studies have been conducted over the years to understand the potential hazards of these two compounds. Piperazine has also been classified and an EU risk assessment report has been written. With regard to AMP and MDEA few studies are available in the literature databases. In this report we have evaluated the toxicity of the amines from single and repeated exposures, including their potential to cause mutations, tumors and birth defects. The toxicology data have been compiled and critically reviewed as far as possible. For each amine either the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL) are indicated. Based on these data we have suggested an exposure guideline for the general population for each of the amines.

Health effects of different amines relevant for CO_2 capture

1 Health effects of monoethanolamine (MEA)

Monoethanolamine (MEA) (CAS number 141-43-5) is a liquid at room temperature. It is completely miscible with water, with a low volatility and possesses an ammoniacal odour. The odour threshold is 5-8 mg/m^3. MEA is a strong base (pH 12.05 of 0.1N aq. sol.), which readily forms salts with inorganic and organic acids. The substance is widely used in industry in the production of soaps and detergents, as a cleaning and cooling agent, as an ingredient in cosmetic formulations, in the synthesis of dyestuffs, in rubber accelerators, and removal of acids gases from atmospheres, such as carbon dioxide from submarines.

The substance is currently classified as:
Xn; R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed) C; R34 (Corrosive, causes burns)

1.1 Toxicokinetics and metabolism

MEA is a normal constituent of the body in both animals and humans. It occurs naturally in a group of phospholipids known as phosphatides. This group of complex lipids is composed of glycerol, two fatty acids, and phosphoric acid linked to the hydroxyl group of glycerol and a nitrogenous base such as choline or MEA (Knaak *et al* 1997).

MEA is absorbed following oral administration, inhalation, and dermal exposure (Binks *et al* 1992). Upon dermal application the major site for the metabolism of MEA is the liver, where it is incorporated into phospholipids. MEA is also distributed to kidneys, lungs, brain and heart. However, the bulk of the dose seems to remain in the epidermis (Gillner and Loeper 1993). Since MEA is a normal constituent in the body, it is also found in human urine. The molecule can be deaminated, the amine excreted as urea, and the carbon may be used as energy source in the body and be oxidized fully to carbon dioxide. Whether MEA is excreted unchanged or metabolized in the urine, depends probably on the concentration in the body. This may be due to saturation of metabolic pathways and suggests that excess levels in the body are not accumulated, but can be directly eliminated via the kidneys.

The fate of ethanolamine-1,2-C^{14} in the intact rat and its tissues has been studied (Knaak *et al* 1997). Most of the dose (54%) was found in the liver, spleen, kidneys, heart, brain and diaphragm, and 12% was accounted for as $^{14}CO_2$ 8 hours after intraperitoneal administration. The radioactivity in tissues was found distributed in lipid, amino acid, organic acid and sugar fractions. Approximately 85% of the tissue radioactivity was found in the lipid fraction. The liver was shown to be the major site for metabolism of MEA followed by the heart and brain.

1.2 Experimental toxicology

Acute toxicity. The acute oral toxicity of MEA has been studied in several laboratory animal species and it appears to be relative low (Knaak *et al* 1997). The oral dose, after which 50% of the animals died (LD50) in rats, was 1.1-2.7 g/kg body weight (bw). Apparently there were no significant sexual or species differences in acute toxicity with respect to MEA. No inhalation LC50 values (air concentration after which 50% of the animals died) have been reported. However, no mortality was registered for rats exposed for 6 hours to substantially saturated vapour concentration of MEA generated at room temperature or to a combination of saturated vapour and mist generated at 170 ^{o}C. The theoretical saturated vapour concentration of MEA at room temperature is 520 ppm (1.3 g/ m^3). Thus, the LC50 seems to be higher than that concentration.

Subacute, subchronic and chronic toxicity. Repeated oral administration to rats for 90 days has indicated a NOAEL of 320 mg/kg bw/day (Binks *et al* 1992). Repeated inhalation of more than 160 mg/m^3 MEA for periods of 24-90 days in several species induced behavioural effects and degenerative changes in different organs, especially in the liver and kidneys (Weeks *et al* 1960). The animals displayed also pronounced clinical signs of skin and respiratory irritation, which progressed with time to hair loss, severe skin lesions, moist rales and fever in dogs and breathing difficulties in rats and guinea pigs (see also below). Effects were observed at all exposure levels and a NOAEL was not found. Repeated inhalation of as low as 30 mg/m^3 MEA for 90 days caused behavioural effects in dogs (progressive stages of excitation followed by depression). Furthermore, rats exposed to 12 mg/m^3 MEA exhibited lethargy after 2-3 weeks exposure (Weeks *et al* 1960). The behavioural changes reported for exposed animals may reflect the extreme irritancy of the MEA atmospheres employed. Weeks *et al* (1960) reported that MEA was at least 10 times more toxic following inhalation than gastrointestinal uptake. There are very limited data available on long-term toxicology.

Irritating properties. The most pronounced acute effects of MEA in animals are those related to the irritant properties. MEA can cause burns and necrosis to the skin following a 4 hours exposure, also eye irritation and irritation of the respiratory tract have been observed (Gillner and Loeper 1993). Exposure of rats, dog and guinea pig to MEA vapour has been reported to induce skin irritation at as low concentration as 12 mg/m^3 (Week *et al* 1960). The authors indicate, however, that this might be due to a direct dermal exposure to MEA as vapour condensed onto the surfaces in the exposure chambers.

Sensitization. No animal studies have assessed the skin sensitization potential of MEA (Knaak *et al* 1997). Repeated-insult skin patch testing of human volunteers or chemical workers has produced negative results. The overall evidence suggests MEA not to be allergenic.

Genotoxicity and carcinogenicity. MEA lacks mutagenic potential in Ames bacterial mutagenicity when tested in the presence or absence of a metabolic activation system with a variety of *Salmonella typhimurium* tester strains developed to identify base-pair substitution or framshift mutagens (Knaak *et al.*

1997). MEA also failed to cause mutations in a test organism that is sensitive to oxidative-type mutagens (*Escherichia coli*). Several assays of the potential of MEA to damage DNA in a bacterial tester strain (*Bacillus subtilis* rec assay) and to cause chromosomal damage in yeast cells (*Saccharomyces cerevisiae* gene conversion assay) have been negative. MEA did not induce chromosome damage in rat liver epithelial-type cells. No *in vivo* genotoxicity studies have been reported. Furthermore, no data on carcinogenicity have been located.

Reproductive and developmental toxicity. In rats MEA is reported to cause significant, dose- dependent intrauterine growth retardation, and increases in malformations and intrauterine deaths after oral administration to the dams during the period of organogenesis (Mankes 1986). These effects were seen down to the lowest dose studied (50 mg/kg bw/day). At this dose level no maternal toxicity was seen. The male offspring were more severely affected than female pups. In another study with rats no effects on organ development or fetal weight were observed even at high doses (450 mg/kg/day) which caused maternal toxicity (Hellwig and Liberacki 1997). Decreased or repressed spermatogenesis was seen in guinea pigs exposed to MEA vapour at about 190 mg/m^3 for 24 days and dogs exposed to about 250 mg/m^3 for 30 days (Weeks *et al* 1960). The significance of this observation is not clear as these concentrations resulted in the death of 75% of the guinea pigs and one of three dogs exposed.

1.3 Human data

Occupational exposure to MEA mainly occurs by inhalation (Gillner and Loeper 1993). The general population may also be exposed by dermal contact to MEA in cosmetic formulations. The effects on humans are related to the primarily irritative local action of MEA. A concentration of 5.9% is irritating to human skin. There have also been reports of occupational asthma and skin sensitization following MEA exposure (Binks *et al* 1992). In a study by Sidorov and Timofievskaya (1979) increased incidence of liver and gall bladder disease and chronic bronchitis in humans at levels as low as 1 mg/m^3 was observed. This study is however criticized due to their poor reporting on number of subjects and duration of exposure. Similarly chronic hepatitis was also found in one subject following an accidental high exposure to MEA. This is difficult to evaluate as the conditions at the time indicate it was a mixed exposure. The other solvents were not specified and no indication of the level of the exposure was given (Binks *et al* 1992).

1.4 Occupational exposure limits

Because of the lack of human data the use of animal studies was necessary to make a health-based exposure limit in the occupational environment (SCOEL 1996). An EU directive from 2006 describes indicative exposure limit values for MEA. The time-weight average (TWA) value for 8 hours is 2.5 mg/m^3 and the short-term exposure limit (15 min) is 7.6 mg/m^3. The 8 hours administrative norm has recently been changed to 2.5 mg/m^3 in Norway (Arbeidstilsynet 2007).

1.5 Health risk evaluation

The study of Weeks *et al* (1960), establishing a LOAEL of 12 mg/m^3 air for behavioural effects in rats seems to be the best available basis for proposing an exposure limit for the population. The same study was also used when establishing the occupational exposure limit (Arbeidstilsynet 2007). Since this LOAEL value is based on an animal experiment, an uncertainty factor has to be used. The occupational exposure limit includes an uncertainty factor of only 5. However, for the general population a factor of 10 is normally applied because of extrapolation from animal studies (rat) and another factor of 10 for the variability between the individuals (in human a population). Use of a LOAEL value instead of a NOAEL should affect the size of the uncertainty factor by a factor of 3, but as the effects seen here were minimal we have decided to use a factor of 2. Furthermore, use of subacute instead of chronic should increase the uncertainty factor by 6. All together, this infers the uncertainty factor to be 1200. Therefore, we suggest that the general population, over time, should not be exposed to levels in the air higher than 10 µg/m^3 MEA.

2 Health effects of piperazine

All data presented are based on information in the EU risk assessment report – piperazine final report, 2005. No relevant health effect data on piperazine were found in a litterature search from 2005 to 2008.

Piperazine (CAS number 110-85-0) is white or translucent, and occurs as rhomboid or flake-like crystals that are highly hygroscopic at room temperature. It is a white mass in water and highly basic with two dissociation constants, pKa1=9.7 and pKa2=5.3. It is used in veterinary pharmaceuticals as anthelmintics, i.e., drugs that act against infections caused by parasitic worms. Formerly, it was also used in human medicine. Other industrial uses of piperazine are as hardener for pre-polymers for glue, in gas washer formulations, as intermediate for urethane catalysts, and as an intermediate for a number of pharmaceuticals.

Classification by EU:

- Repr. Cat. 3; R62-63 (Possible risk of impaired fertility/harm to the unborn child)
- C; R34 (Corrosive; Causes burns)
- R42/43 (May cause sensitisation by inhalation and skin contact)
- Labelling:
- Xn; C
- R: 34-42/43-62-63

2.1 Toxicokinetics and metabolism

Piperazine is readily absorbed from the gastrointestinal tract in pigs, and the major part of the compound is excreted as unchanged piperazine during the first 48 hours. The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16%). However, about one forth of a single administered oral dose is retained in the tissues after 7 days, some of which seems to consist of unidentified conversion products. Besides N-

mononitrosopiperazine, no other metabolites have been identified. No data on dermal or respiratory uptake have been located. Default absorption values of 100% are assumed for dermal and inhalation exposure.

In humans the kinetics of the uptake and excretion of piperazine and its urinary metabolites appear to be roughly similar to that in the pig, but the nature and extent of conversion to metabolites remains unknown. In the presence of nitrite, the *in vivo* formation of small amounts of nitrosated products from piperazine has been demonstrated to occur in the gastrointestinal tract of experimental animals as well as in humans.

2.2 Experimental toxicology

Acute toxicity. Piperazine has demonstrated a relatively low acute toxicity (LD_{50} 1-5 g/kg bw) by the oral, dermal, and subcutaneous route of administration to rodents, whereas adequate inhalation toxicity data could not be located.

Subchronic and chronic toxicity. Upon repeated dose oral administration to rats and dogs, except for some signs of liver toxicity, little evidence of systemic toxicity was observed even at the highest tested dose. Based on induction of mild hepatic involvement in the Beagle dog a NOAEL of 25 mg/kg bw/day of piperazine base was established. Although inadequately reported, a 90 day study in rats indicates an approximate LOAEL of 150 mg/kg bw/day based on histopathological changes in liver and kidneys. The NOAEL in beagle dog was chosen by EMEA (The European Agency for the Evaluation of Medical products) as the basis for setting an acceptable daily intake (ADI) and provisional maximum residual levels (MRLs) for the use of piperazine as a veterinary anthelmintic in pigs and poultry (EMEA, 2001a). Adequate chronic bioassays are not available. None of the animal experimental studies reported neurotoxic effects as a cause for serious concern. However, such effects, that occasionally are serious, have been well documented in clinical practice, and have also been described by veterinarians in rabbits, dogs, cats, tigers, horses, the puma, and sea lions, but not in rodents. The mechanism of the neurotoxicity induced by piperazine in mammals is unknown. Although it may be assumed that similarly to its action in invertebrates, it acts as a neurotransmitter. The inability to detect any signs of such toxicity in available subacute and subchronic studies is a reason for concern, and makes it impossible to establish a LOAEL or NOAEL with respect to this important toxicological endpoint. It is established beyond doubt that piperazine after 1-7 administrations induces neurotoxicity in some mammalian species including humans, among which children appear to be particularly sensitive. Hence, this end-point has not been adequately investigated.

Irritating and corrosive properties. In rabbits, a 50% aqueous solution of piperazine base (i.e., piperazine anhydrate) has strongly irritating properties, including induction of skin necrosis. At a concentration of 11%, piperazine base may induce erythema and marked vesiculation on human skin, whereas no effects were observed at a concentration < 2.2%. Piperazine base and piperazine hexahydrate may cause etching and necrosis of the rabbit eye at a concentration of 1-5% and should be regarded as corrosive (Carpenter and Smyth, 1946). Existing biological data on the corrosive properties of piperazine are corroborated by its

high pH in aqueous solutions. Piperazine is currently classified with R34, which applies for piperazine base and piperazine hexahydrate. No corrosivity is expected for piperazine salts.

Sensitization. Exposure to piperazine and its salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation, but no NOAEL can be set as no threshold could be deduced from these studies. Dermal sensitisation is also shown in the mouse local lymph node assay. A cross-sensitisation between piperazine and diethylentriamine was observed in guinea pigs. It must be concluded that piperazine is a dermal and respiratory sensitizing agent.

Genotoxicity and carcinogenicity. Studies conducted *in vitro,* as well as *in vivo* indicate that piperazine does not induce point mutations or chromosome aberrations (in the Ames test, in a non-standard study on Saccharomyces cervisiae and in Chinese hamster ovary cells). Due to the likelihood of exposure to other clastogenic chemicals, the significance of the modest increase in micronuclei seen in one cohort of exposed workers cannot be ascertained. However, nitroso-piperazines that can be formed by nitrosation of piperazine *in vivo* demonstrate clear genotoxic properties (*in vivo* DNA strand breaks and mutations).

There are no solid indications of a carcinogenic effect of piperazine, neither in animal studies, nor from the investigation in humans. However, the supporting database is insufficient to permit definite conclusions. The two nitrosated derivatives of piperazine, N-mononitroso-piperazine and N,N'-dinitrosopiperazine, whereof the first has been identified as a minor metabolite of piperazine, have in addition to induce mutations *in vivo,* and also been found to be carcinogenic in rodents.

Reproductive and developmental toxicity. For reproductive effects based on data from a two generation rat study (Wood and Brooks, 1994), a NOAEL of 125 mg/kg bw/day and a LOAEL of 300 mg/kg bw/day piperazine can be established, based on reduced pregnancy index, decreased number of implantation sites and decreased litter size. The decreased litter size is evaluated as the main effect. The NOAEL for the adult animals is estimated to be 125 mg/kg bw/day piperazine base. This NOAEL is based on body weight decreases (<10%) at 300 mg/kg bw/day in the parental males and in the offsprings.

The developmental toxicity has been investigated in rats and rabbits in adequate studies. In rabbits, embryotoxic as well as teratogenic effects were elicited only at doses that also caused overt signs of toxicity in the mother animal (maternal LOAEL/NOAEL, 94/42 mg/kg bw/day, respectively).

3 Human data

Acute toxicity. Neurotoxic changes as examined by EEG have been reported in 37% of 89 children administered 90-130 mg/kg/bw piperazine base (two doses during one day), corroborated by the proposed function to piperazine as a neurotransmitter. Since more severe neurotoxicity symptoms can appear after

exposure to higher doses (given during several days), a LOAEL of 110 mg/kg bw for neurotoxicity in humans after acute exposure is proposed.

Subchronic and chronic toxicity. For previously healthy humans, a LOAEL of 30 mg piperazine base/kg bw/day for neurotoxicity has been established for a limited treatment period (3-7 days). Since there is little information on effects at lower doses than the therapeutic dose, the 30 mg/kg bw/day dose should rather be regarded as a 'low OAEL' than a true LOAEL. Based on existing data, a NOAEL cannot be established for neurotoxicity induced by piperazine, neither in a sensitive animal species nor in humans upon long-term exposure. In humans, repeated exposure to piperazine by inhalation may induce chronic bronchitis, but no LOAEL or NOAEL can be established for this endpoint.

Irritating and corrosive properties. Six occupational exposure scenarios concerning production of piperazine flakes and piperazine salts, and industrial use of piperazine in syntheses have been considered. Worst-case exposure is assumed for the scenarios on production and industrial use, by using monitored data when available, and otherwise modelled values for inhalation exposure and dermal exposure.

Sensitization. Exposure to piperazine and its salts has clearly been demonstrated to cause asthma in occupational settings. No NOAEL can be estimated for respiratory sensitisation (asthma). The external worker exposure inducing occupational asthma by inhalation has been estimated to be up to 8.6 mg/ m^3 during normal work for an 8-hour day.

Reproductive and developmental toxicity. There is one case report available, describing the birth of a girl with malformed hands and feet as a possible result of piperazine exposure of the mother (Keyer and Brenner, 1988). The mother was treated orally with piperazine adipate (2,100 mg/day or 38 mg/kg/day assuming a body weight of 55 kg) during two 7-days periods. At birth, both hands and one foot displayed malformations. It is difficult to evaluate the possible relationship with the piperazine treatment from this only case.

3.1 Occupational exposure limits

Commission Directive 2000/39/EC (European Commission, 2000) establishes a first list of indicative occupational exposure limit values. The values for piperazine concerning vapour and dust are 0.1 mg/m^3 for 8-hour exposure and 0.3 mg/m^3 for short-term exposure (based on a study by Hagmar *et al.*, 1982). The list was implemented in EU member states 31 December 2001.

3.2 Health risk evaluation

For neurotoxicity, a LOAEL in healthy humans of 30 mg/kg bw/day piperazine base for a limited 3-7 days exposure has been established. A NOAEL of 25 mg/kg bw/day for induction of mild hepatic involvement in the Beagle dog has also been established. Furthermore, a LOAEL for inducing occupational asthma after inhalation of piperazine has been estimated to be 8.6 mg/m^3 during normal work for an 8-hour day.

The estimated exposure from human inhalation studies of 8.6 mg/m^3 will be used in the risk estimation below. This is due to the anticipation that the main route of exposure of amines for the general population will be via inhalation. Exposure to piperazine and its salts has clearly been demonstrated to cause asthma in occupational settings. No NOAEL can be estimated for respiratory sensitisation (asthma). However, the external worker exposure by inhalation has been estimated to be up to 8.6 mg/m^3 (vapor and dust) during normal work for an 8-hour day. For short-term exposure (15 minutes), the concentrations may be twice the above mean value. The study by Hagmar et al., 1982 showed occupational asthma measured at lower concentrations than the estimated exposure level described above. However, the exposure levels could only be roughly estimated and the LOAEL as well as NOAEL for asthma induction in this cohort is, therefore, associated with too much uncertainty to be brought forward to the risk evaluation.

The exposure indications of amines released to the environment is expected to be high and this suggests that Piperazine represents a risk for man exposed via environment. It is clear that piperazine is a respiratory sensitiser and based on the presented data we choose the external worker exposure estimated exposure value of 8.6 mg/m^3 as a LOAEL. For the risk evaluation there is considered a need for the use of uncertainty factors. A factor of 10 for the variability between the individuals in a population is used. Both a factor of 3 for extrapolation from a LOAEL to a NOAEL and an exposure factor for subchronic to chronic of 2 are included. In addition a correction factor for work exposure versus lifetime exposure of 2.8. As there are findings of both neurotoxicity, mild hepatic toxicity and reproductional effects in human and animal studies, we have also included a factor of 10 for severe health effects (neurotoxicity). Together the uncertainty factor will be 1680. Therefore, we suggest that the general population should not, over time, be exposed to higher levels than 5 µg/m^3 piperazine base.

4 Health effects of aminomethylpropanol (AMP)

The report of AMP is mainly based on the "Final report on the safety assessment of aminomethylpropanol and aminomethylpropanediol" in the Journal of the American College of Toxicology Volume 9 Number 2 1990 and an IUCLID report from 2000. Most of the studies referred to in these reports are unpublished and have therefore not been available to us. Hence, this report is based on previous evaluations performed by others. In general, data for AMP were limited.

AMP is also known as isobutanolamine and 2-amino-2-methyl-1-propanol (CAS number 124-68-5). AMP is either a colourless liquid or a white crystalline solid. Since the melting point is slightly above room temperature AMP may also appear as a paste. In liquid form AMP has a slight amine-like odour, while in solid form it is odourless. AMP is miscible with water, soluble in alcohols, slightly soluble in aromatic hydrocarbons, and insoluble in aliphatic hydrocarbons (CIR 1990). The pKa for AMP is 9.7 at 25˚C (IUCLID 2000).

AMP is widely used in cosmetics, as an emulsifying agent, as a pH adjuster and to regulate the solubility, flexibility and tackiness in cosmetic creams, lotions, soaps,

shampoos, shaving creams, hair sprays, hair dyes and colours and more. The content of AMP in cosmetic is most commonly in the range of 0.1% - 1% with a few products containing more than 1% AMP. In non-cosmetic products AMP has been used in leather dressings, cleaning compounds and polishes, insecticides, paints, antibacterial agent and as an indirect food additive. Products containing AMP may come in contact with the skin, eyes and mucous membranes. The exposure may be temporary or prolonged and for many products the exposure is repeatedly over a period of time (CIR 1990).

The substance is currently classified as:
Xi; R36/38 (Irritating to eyes and skin)

4.1 Toxicokinetics and metabolism

AMP has been found to interfere with the formation of free fatty acids from lipids. AMP injected intraperitoneally in rats fed a choline-deficient diet (choline deficiency inhibits "fat removal") caused inhibited fat catabolism and increased amount of hepatic lipid and an increased fat content of the liver. The authors suggested that AMP, or metabolites of AMP, might become incorporated into phospholipids and inhibit the incorporation of ethanolamine which will result in a reduced conversion of choline and consequently increase the amount of lipids in the liver (CIR 1990).

AMP is rapidly and completely absorbed from the gastrointestinal tract in rats (Saghir et al. 2008). The maximal blood concentration was reached within 15 minutes of dosing and only 3-4 % of the administrated dose was found in the tissues 168 hours post dosing. The highest dose level was found in the liver and kidney. Between ~ 90% of the AMP dose was eliminated by urine and most (~75%) within the first 48 hours. Faecal elimination accounted for only 3-10%. The elimination of AMP after oral administration occurred via two phases. Most of it was rapidly eliminated (α elimination). The level in blood was reduced by 7-9 folds in a 4-hour period. Thereafter the elimination was slower, which is suggested to include elimination of AMP that has been incorporated into phospholipids and other cellular fractions. AMP is excreted unchanged. No metabolites have been found in blood or excreta which are suggested to be due to steric hindrance and a fairly stable structure of AMP (Saghir *et al* 2008).

Dermal absorption of AMP in rats has been found to be relatively high, but slower compared to oral administration. Saghir *et al*. found that the total dermal absorption of AMP was 42% which included ~ 8% of the dose remaining at the application site 162 hours after washing. Less than 1% of the dose remained in the stratum corneum. Approximately 6% of the applied dose was found in the various tissues with a distribution similarly to that of the orally dosed rats. Most of the administrated dose was eliminated by the urine (43%) (Saghir *et al* 2008).

4.2 Experimental toxicology

Acute toxicity
The LD50 for rats and mice were 2.9 and 2.15 g/kg bw, respectively (Anon 2007; CIR 1990; IUCLID 2000). In an acute toxicity study in rats AMP caused lesions in the liver, kidneys, spleen and lungs at LD50 dose. In another acute oral study in

rats, no effects caused by AMP were found. In a study with monkeys AMP solution had toxic effects on the gastrointestinal tract, but the effect was most likely due to the alkalinity (pH>11) of the AMP solution (CIR 1990).

In the IUCLID dataset dermal LD50 was found to be > 2 g/kg bw in rabbits. The study followed GLP, but no further information was given (IUCLID 2000).

The LD50 for mice given AMP intraperitoneally was found to be 325 mg/kg bw. The study is from 1955 and does not follow GLP (IUCLID 2000).

No LC50 was noted in the IUCLID dataset. In the CIR report on AMP three acute inhalation studies with cosmetic formulations containing AMP and one inhalation study with AMP in alcohol and propellant was described. The highest concentration tested was 200 mg/l of a 2.5% AMP solution (one hour exposure time). By necropsy one animal in two separate studies showed abnormalities in the lungs. In a separate study two females had tremors upon removal from the test chamber. The rats appeared normal after 24 hours. No significant histological changes were observed. The CIR 1990 report concluded that the observed effects were not related to treatment and that the results of the studies indicated that AMP was nontoxic by inhalation.

Subacute, subchronic and chronic toxicity
In a 28-days range finding study one beagle dog of each sex were given AMP in the diet at concentrations of 600, 1800, 5400 and 16200 mg/kg. In the three highest doses dogs had frequent soft stools and diarrhoea. Both dogs of the highest dose group had marked weight loss, anorexia and dry noses and mouths. Damage to the liver and reduced liver weight was dose-dependent (CIR 1990).

In an eight weeks study 10 mice of each sex were given AMP in the diet at concentrations of 200 to 3200 mg/kg. At the end of the experiment, all mice appeared normal. No gross or microscopic lesions were found in the liver. NOAEL was set to > 3200 mg/kg (Anon 2007; CIR 1990).

In a similar study with rats the same test protocol as in the mouse study was used, except that the dietary concentration were 1000, 2000, 4000, 8000 and 16000 mg/kg. The rats given the highest dose were emaciated and had rough hair coat, small skin lesions and loss of hair. Two females in the highest dose group died before the end of the study. Alopecia and focal skin erosions were observed in rats given the highest dose. Hepatocyte vaculation was observed in rats at all doses and was considered compound-induced. The LOAEL was suggested to be 1000 mg/kg (Anon 2007; CIR 1990). In a 90-days study with rats AMP solutions with pH 7 and 11 were tested. It was concluded that the mortality observed was caused by the alkalinity of the solution and not by AMP *per se* (CIR 1990). In a 90-days study four male and four female beagle dogs were fed diets containing 0.63, 15.0, or 62.5 mg AMP/kg bw (pH 7). Only the dogs of the high-dose group did not gain weight during the study. Also liver and liver/body weights ratios were increased and tan and mottled livers were observed by necropsy in the high-dose group. Vacuolisations and lipid deposits in the liver, and bile duct hyperplasia were observed by microscopic examination in all dogs at the high dose and one dog at the mid dose (CIR 1990). Based on liver effects the NOAEL was set to 0.63

mg/kg bw/day. However, in a one year dog study reported in IUCLID (2000) the NOAEL was considered to be much higher (≥ 100 mg/kg bw).

Generally it was not noted whether the concentrations of AMP used in the inhalation studies were the highest attainable or not. No per cent inhalable aerosols were given and the exposure time and strategy varied. Since most of these studies are performed with cosmetic solutions containing AMP it is also difficult to interpret whether the observed effects are caused by AMP alone or by the combination of AMP in the solution.

An inhalation study was preformed with hair spray containing 0.58% AMP solution. Rats were exposed to the atmosphere containing 200 mg/l of the hair spray (1 hour/day, 5 days per week for 2 weeks). No gross changes were noted at necropsy, and weight gains were comparable between the test animals and the control group (CIR 1990).

Three inhalation 90-days studies have been performed; one study with rats and two with monkeys. In all studies pump hair spray containing AMP was used. Rats exposed to 0.44% AMP solution in a concentration of 0.23 μg/l had statistically significant hematologic changes compared with the control. However, the laboratory claimed that the changes were within the normal range for this species. It was observed that female rats had significantly decreased uterine and lung weights and increased heart- and liver-to-body weight ratio. No treatment-related microscopic changes were observed in the evaluated tissues. In a study where monkeys were exposed to 6.06 and 6.63 μg/l of a hair spray containing 0.40% AMP, no compound-related alterations of the tissues were found upon histopathological examination. However, reduced weight gain during the study was observed. In the second study monkeys were exposed one hour daily to 2.7 or 27 μg/l of a hair spray containing 0.21% AMP. Some histopathologic changes in the pulmonary tissues and pulmonary alveolitis were noted in the high-dose group. A slight to moderate increase of hepatocellular lipids were observed in all animals (CIR 1990).

Irritation

AMP has been classified as an irritant to eyes and skin (IUCLID, 2000). In a data sheet for AMP coughing and sore throat were also noted (IPCS 2002). In the CIR of 1990 several dermal irritation studies are described. Only in two of the studies AMP caused mild irritating to the skin. Cosmetic formulations containing 0.22-0.56% AMP were used. Also several eye irritation studies were described. AMP was given in different formulations containing 0.22-0.58% with various exposure strategies. In some of the studies AMP caused eye irritation to some animals. In one study the irritation observed was classified as a mild irritation according to the Draize classification system (CIR 1990; IUCLID 2000).

Sensitisation

AMP was tested in a Bhuler test (1982, GLP) and was not found to have sensitisation potential (IUCLID 2000).

Genotoxicity and carcinogenicity
A plate assay mutagenicity test was performed using AMP and *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, 1537, 1538, 98 and 100. The results indicated that AMP was not mutagenic, with and without metabolic activation (CIR 1990; IUCLID 2000). AMP was tested in a one year study with dogs. No evidence of any preneoplastic lesions was found and the data suggest that AMP is not carcinogenic (Anon 2007).

Reproductive and developmental toxicity
In a recent rat reproductive/developmental screening study, the HCl salt of AMP was found to be fetotoxic in rats. The study was performed in 2005 according to OECD guideline 421. Male and female rats were fed diets containing 0 (control), 100, 300 or 1000 mg AMP-hydrogen chloride/kg bw/day. Evidence of complete litter resorption (100% post-implantation loss) was seen at 1000 mg/kg bw/day, and significant resorptions were seen at 300 mg/kg bw/day. In rats given 300 mg/kg bw/day decreased litter size, increased pup body weight and decreased gestation body and body weight gain were observed. The NOAEL for systemic toxicity for males (parent generation) was 100 mg/kg bw/day. NOAEL for females (parent generation) could not be established due to liver effects in the lowest dose group. The NOAEL for reproductive toxicity was considered to be 100 mg/kg bw/day (Anon 2007).

In a developmental study performed in 2006 in accordance with OECD guideline 414, female rats were dermally exposed six hour daily to 0, 30, 100 or 300 mg AMP/kg bw/day during gestation days (day 6 post mating to day 20). Dermal findings at 30 and 100 mg/kg bw/day were not considered adverse. NOAEL for maternal toxicity based on dermal effects was 100 mg/kg bw/day. AMP did not cause any systemic or developmental toxicity at any dose level tested. The NOAEL for developmental toxicity was considered to be 300 mg/kg bw/day (Anon 2007).

4.3 Human data

Skin irritation and sensitisation potential has been examined in humans. Fifteen persons tested a cosmetic formulation containing 0.22% AMP using a single insult occlusive patch test. One person had an equivocal reaction and it was concluded that AMP had a negligible primary skin irritation potential (CIR 1990). In a sensitisation study 97 persons were exposed to different AMP formulations for three weeks. Thirteen persons had weak reactions during induction phase and one person had a weak reaction after challenge. This result supports the negative finding in the Bhuler test from 1982 indicating that AMP is not a sensitizer.

4.4 Health risk evaluation

To suggest a maximal exposure level for the general population two 90-days studies are possible to use. Both studies have limitations and no one is optimal. In the oral dog study, there are uncertainties of the dose given, while in an inhalation study with monkeys, AMP was given in hair spray which may influence the effect of AMP.

In the 90-days inhalation study, monkeys were exposed one hour daily to 2.7 or 27 μg/l of hair spray containing 0.21% AMP. Effect on the target organ (liver) was observed at both dose levels. The LOAEL was set at 2.7 μg hair spray/l which compares to 0.57 mg AMP/m^3air. An uncertainty factor of 5 for the variability between species (monkeys to humans), an uncertainty factor of 10 for variations in the human population and an uncertainty factor of 2 for using a subchronic study instead of a chronic study were included. Together the uncertainty factor is 100. Based on this, it is suggested that the general population, over time, should not be exposed to higher levels of AMP in the air than 6 μg/m^3. We have also calculated a maximal exposure level based on a 90-days beagle dog feed study. Unfortunately this study is unpublished and it is incomplete referred to in the report (CIR 1990). However, the data indicate that if the maximal exposure level for the general population is calculated based on the dog study, the level will be higher than 6 μg/m^3. Occupational exposure limits has not been found for AMP.

5 Health effects of methyldiethanolamine (MDEA)

Methyldiethanolamine (MDEA) (CAS number 105-59-9) is a liquid at room temperature with an ammonia-like odour. It is completely miscible with water and has a low volatility (vapour pressure 0.001 torr, 25 ºC). MDEA is used e.g. as a gas treating agent for absorption and removal of H_2S and CO_2, a urethane catalyst, a textile softener, an epoxy curing agent and in pH control.

The substance is currently classified as:
Xi; R36 (Irritating to eyes)

5.1 Toxicokinetics and metabolism

The toxicokinetics of radiolabeled MDEA was studied in rats after intravenous (50 and 500 mg/kg bw) and cutaneous (500 mg/kg bw) dosing (Leung HW *et al* 1996). MDEA was readily absorbed following dermal application. The absorption was 17 – 21% and 41 – 50% after 6 and 72 hours of contact, respectively. Once absorbed from the skin surface, MDEA appeared to be sequestered in the skin matrix as evidenced by its delayed and steady release into the bloodstream. The highest concentrations of radiolabel were found in the liver and kidneys. Elimination was primarily through the urine, with an excretion half-life in excess of 30 hours after dermal application. MDEA was extensively metabolized at lower doses. However, nonlinear kinetic behaviour following intravenous administration of 500 mg/kg bw suggests saturation of metabolism at high doses.

Leung *et al* (1996) hypothesise that MDEA, like diethanolamine (DEA), could be incorporated into membrane phospholipids to form aberrant sphingomyelins by following the biosynthetic route common to ethanolamine. This may explain in part the temporary storage in the skin and the delayed appearance of radioactivity in blood.

5.2 Experimental toxicology

Acute toxicity
A report on acute toxicity and primary irritation of 5 alkylalkanolamines, including MDEA has been published (Ballantyne and Leung, 1996). In this report the oral LD_{50} for Sprague-Dawley rats was found to be 1.9 g/kg bw (1.87 ml/kg bw, gavage). There were no significant differences between males and females.

Dermal LD_{50}s were 10.2 g/kg bw (9.85 ml/kg bw) and 11.34 g/kg bw (10.90 ml/kg bw) in a 24 hour study in male and female rabbits, respectively. Dermal effects included moderate to severe erythema and edema with ecchymoses, necrosis, and ulceration. These effects persisted and progressed to local desquamation, alopecia, and scarring by the end of the 14 days observation period. Necropsy of animals that died revealed dark red mottled lungs, dark red livers, and mottled kidneys.

Rats were exposed to a saturated vapour atmosphere for 6 hours. No mortalities and no significant signs of toxicity were reported.

In addition, several unpublished acute toxicity studies are mentioned in IUCLID (2000). The LD_{50}-values cited support the conclusions that MDEA is of relatively low acute oral and percutaneous toxicity. Furthermore, unpublished mice studies with intraperitoneal exposure resulted in LD_{50}-values between 500 and 666 mg/kg bw.

Irritating properties
MDEA was found to be mildly irritating to the skin (502 mg or 500 µl) and to the eyes (5 µl) of rabbits (Ballantyne and Leung, 1996). Application to the skin for 4 hours produced mild erythema and edema (lasting about two days) accompanied by a few scattered ecchymoses. In the eye, a slight to moderate conjunctival hyperemia and chemosis was observed and resolved itself within three days. A slight corneal opacity was observed at 24-hours post-treatment in one of six rabbits.

Several rabbit dermal and eye irritation studies are cited in IUCLID (2000) reporting effects ranging from non-irritating to moderately irritating to skin and from moderately irritating to irritating to eyes.

Sensitization
The skin sensitization potential of 4 alkylalkanolamines, including MDEA, has been tested in the guinea pig maximization assay (Leung and Blaszcak, 1998). MDEA was found to be irritating to skin in an undiluted form, but did not induce a sensitization response.

Subacute, subchronic and chronic toxicity
Repeated-dose studies (2 short-term and 1 subchronic) investigating local and systemic toxicity of dermally applied MDEA in rats are reported by Werley *et al*, 1997. The first short-term study exposed rats to 0, 260, 1040, or 2080 mg/kg bw/day of undiluted MDEA for 9 days, 6 hours/day. Apparently due to local

toxicity and effects on body weight, a second short-term study was performed with doses of 0, 100, 500 or 750 mg/kg bw/day of aqueous dilutions of MDEA for 9 days, 6 hours/day. In the subchronic study, rats were dosed with 0, 100, 250 and 750 mg/kg bw/day of an aqueous dilution of MDEA (5 days/week, 6 hours/day over 13 weeks).These repeated dose studies resulted in dose/concentration-related skin irritation, and slight changes in weight gain, adrenals gland weight, hematological and clinical chemistry changes. Histopathological findings were limited to treated skin. According to Werley *et al*, 1997 the highest dose in the sub-chronic study (750 mg/kg bw/day) did not induce adverse systemic toxicity and can thus be considered a systemic "no observed adverse effect level" (NOAEL), whereas local skin irritation was seen from doses exceeding 100 mg/kg bw (equivalent to a concentration of 100 mg/ml; 10% solution). However, the hematological and clinical observations for the subchronic study were not provided in the article. In addition, it is not clear whether histopathological examinations of presumed target organs (liver and kidneys) were performed.

No repeated dose study with a non-dermal exposure route, and no chronic toxicity study have been found in the literature search.

Genotoxicity
MDEA was non-genotoxic when tested in the presence and absence of a metabolic activation system in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and/or TA97 (Zeiger et al., 1987). A more recent genotoxicity study has been performed in which several genotoxicity assays were used. In this study, MDEA did not induce reproducible, significant or dose-related increases in the frequencies of mutations, sister chromatid exchanges or micronuclei (Leung and Ballantyne, 1997). Some additional in vitro genotoxicity studies are mentioned in IUCLID (2000). Together these results indicate that MDEA is not genotoxic.

Carcinogenicity
No carcinogenicity or chronic toxicity studies with MDEA have been found. Although MDEA is not considered genotoxic, the structurally similar substance diethanolamine (DEA) has been reported to induce tumours in mice. Whether MDEA has a carcinogenic potential via a non-genotoxic mechanism, is a possibility which should therefore not be excluded. Non-genotoxic carcinogens are assumed to have an exposure threshold, below which there is generally no reason for concern.

The following discussion about the mechanism of the carcinogenicity of DEA is partly based on the "Report on carcinogens. Background document for diethanolamine", prepared for the National toxicology program in 2002. DEA, like MDEA, is not genotoxic, but induces liver and kidney tumours in B6C3F1 mice. However, DEA was not carcinogenic in Fisher 344 rats or in a transgenic mouse strain (Tg·AC). As DEA and MDEA are very similar substances and MDEA is probably formed during the metabolism of DEA it can not be excluded that MDEA has carcinogenic properties. Potential mechanisms of DEA induced carcinogenicity include its conversion to a carcinogenic nitrosamine, *N*-nitrosodiethanolamine (NDELA), which occurred *in vivo* in rats simultaneously administered DEA dermally and nitrite orally. However, it is questionable

whether the metabolite NDELA explains the hepatocarcinogenisity observed in B6C3F1 mice. The second proposed mechanism involves the displacement of ethanolamine by DEA in phospholipids, an effect that may result in a reduced endogenous production of choline. Observations on the effects of DEA on choline metabolism support the proposal that DEA-induced hepatocarcinogenesis may be related to choline deficiency.

Reproductive and developmental toxicity
No fertility study has been identified.

One developmental study has been found. In this study rats were exposed via the dermal route to aqueous dilutions of MDEA (0, 250, 500, and 1000 mg/kg bw/day, 6 hours/day during gestation days 6 to 15). No adverse effects on any gestational parameter or increase in the incidence of malformations or variations were reported. No differences in maternal body weight, gestational weight gain, food consumption or liver, kidney, or gravid uterine weight were observed at any dose group. Maternal toxicity was apparent as a mild anaemia in dams at the 750 and 1000 mg/kg bw/day dose group. Skin irritation occurred at the 1000 mg/kg bw/day, and increased in severity with time. The NOAELs for maternal toxicity and embryofetal toxicity and teratogenicity were estimated at 250 and at or above 1000 mg/kg bw/day, respectively (Leung and Ballantyne, 1998).

5.3 Human data

Alkanolamines, including MDEA, are often added as borates to metal-working fluids (MWFs). Alkanolamines may contribute to irritation as well as allergic contact dermatitis in workers from MWFs. A study examining responses in dermatitis patients to patch testing to components of MWFs, including MDEA has been published (Geier et al, 2003). Seven of 233 patients reacted positively and one of these patients had a reaction to MDEA. The authors state that the importance of MDEA as a MWF allergen remains to be established.

5.4 Occupational exposure limits

Occupational exposure limits exist for several alkanolamines, but has not been found for MDEA. An internal company limit value of 10 ppm (approximately 49 mg/m^3) was given in IUCLID (ICI C&P France SA, IUCLID 2000).

5.5 Health risk evaluation

The available studies indicate local irritation of skin and eyes following exposure to MDEA. In the subchronic, dermal study it is indicated that irritation occurs at concentrations higher than 10%. However, eye irritation seems to be more severe than skin irritation and may thus be present at lower concentrations of MDEA. MDEA is likely to be irritating also to the respiratory tract. However, there is very little information on the inhalation toxicity of MDEA. It is important that the concentration of MDEA in air is well below levels probable to induce respiratory irritation.

The current health risk evaluation of systemic toxicity is based on the toxic effects seen in the repeated dose toxicity studies. The lowest systemic NOAEL (dermal dose) identified was 250 mg/kg bw/day, resulting in mild anaemia in dams in the

developmental study. In order to suggest a safe ambient air level with regard to systemic toxicity we have performed an extrapolation from the dermal dose to an internal body dose. The concentration in air that will result in a similar internal dose was then calculated and appropriate uncertainty factors were applied. For the conversion of the dermal NOAEL to an internal dose a 17% absorption value was used resulting in an internal NOAEL of 42.5 mg/kg bw/day. A human inhalation volume of 25 m^3/24 hours (light activity) and 70 kg bw was used to calculate the air concentration that may give rise to an internal exposure of 42.5 mg/kg bw/day, assuming 100% absorption of MDEA via the respiratory tract. An uncertainty factor of 1000 was used to account for intra- and interspecies variations (100), as well as for the extrapolation from a 7 day study to the chronic situation (10). Based on the above mentioned systemic effects, we suggest that the general population, over time, should not be exposed to higher ambient air levels of MDEA than 120 µg/m^3. However, some alkanolamines may have a carcinogenic potential as has been reported for DEA. Since there were no chronic repeated dose studies for MDEA available and the possible nitrosamines formed are not yet identified, this endpoint cannot be properly evaluated at the present time. Furthermore, there are no fertility studies available.

6 Concluding remarks

The toxicity studies of the amines, MEA, piperazine, AMP and MDEA, have been evaluated. Among these amines piperazine has been through the most thorough evaluation and classification in the EU system. There are several experimental studies available on MEA, but the majority was performed during 1960 and -70. For AMP and MDEA the toxicological data are generally sparse and good quality inhalation studies are lacking.

All the amines seem to be irritative, but only piperazine is reported to be sensitizing. For piperazine and MEA there are indications of reproductive and developmental toxicity. In addition data from one study suggests similar effects of AMP, but this has to be confirmed by other studies. None of the amines have been reported to be carcinogenic, but this should also be evaluated further with additional studies.

The suggested exposure guidelines for the amines are based on the available literature; particularly for AMP and MDEA there are few high quality studies. The guidelines presented here should therefore be used as an indication and not as limit values for safety. The uncertainty factors were chosen in accordance with EU guidelines. Furthermore, use of more than one amine infers that the exposure guidelines should be evaluated again, since the amines seem to have similar adverse effects and might therefore also show additive or synergistic effects.

7 References

MEA:

Arbeidstilsynet (2007) Grunnlaget for fastsettelse av administrative norm for 2-etanolamin.
URL: http://www.arbeidstilsynet.no/binfil/download.php?tid=46041

Binks, S.P., Smillie, M.V., Glass, D.C., Fletcher, A.C., Shackleton, S., Robertson, A.S., Levy, L.S. and Chipman, J.K. (1992) Occupational exposure limits. Criteria document for ethanolamine. Luxemburg, Commission of the European Communities (Report EUR 14240 EN).

Gillner, M. and Loeper, I. (1993) Health effects of selected chemicals 2. Ethanolamine. København, Nordic Council of Ministers (NORD 1993:29) pp. 49-73.

Hellwig, J. and Liberacki, A.B. (1997) Evaluation of the pre-, peri-, and postnatal toxicity of monoethanolamine in rats following repeated oral administration during organogenesis. *Fundam. Appl. Toxicol., 40*, 158-162.

Knaak, J.B,. Leung, H.W., Stott, W.T., Busch, J. and Bilsky, J. (1997) Toxicology of mono-, di-, and triethanolamine. *Rev. Environ. Contam. Toxicol., 149*, 1-86.

Mankes, R.F. (1986) Studies on the embryopathic effects of ethanolamine in Long-Evans rats: preferential embryopathy in pups contiguous with male siblings in utero. *Teratogen. Carcinogen. Mutagen., 6*, 403-417.

SCOEL (1996) Recommendation from Scientific Expert Group on Occupational Exposure Limits for Ethanolamine. (SCOEL/SUM/24) pp. 66-68.
URL: http://ec.europa.eu/employment_social/health_safety/docs/sum_024.pdf

Sidorov, K.K. and Timofievskaya, L.A. (1979) Data for the established of a maximum admissible concentration for monoethanolamine in the workplace air. *Gigiena Truda I Professional'nye Zabolevanija, 23*, no. 9, 55.

Weeks, M.H., Downing, T.O., Musselman, N.P., Carson, T.R. and Groff, W.A. (1960) The effect of continous exposure of animals to ethanolamine vapour. *J. Am. Ind. Hyg. Assoc., 21*, 374-381.

Piperazine:

Carpenter, C.P. and Smyth, H.F. (1946) Chemical burns of the rabbit cornea. *Am. J. Ophtalmol., 29*, 1363-1372.

EU (2008) Commission directive 2008/58/EC of 21 August 2008 amending, for the purpose of its adaptation to technical progress, for the 30th time, Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling

of dangerous substances. Annex 1G. *Off. J. Eur. Com., L 246*, 15.9.2008, 137-190.
URL: http://ecb.jrc.ec.europa.eu/documents/Classification-Labelling/DIRECTIVE_67-548-EEC/ATPS_OF_DIRECTIVE_67-548-EEC/30th_ATP.pdf

European Agency for the Evaluation of Medicinal Products (1999) Committee for Veterinary Medicine Products Piperazine summary report. London (EMEA/MRL/531/98-Final).
URL: http://www.emea.europa.eu/pdfs/vet/mrls/053198en.pdf

Hagmar, L., Bellander, T., Bergöö, B. and Simonsson, B.G. (1982) Piperazine-induced occupational asthma. *J. Occup. Med., 24***,** 193-197.

Meyer, M.M. and Brenner, P. (1988). Spalthand- und Spaltfußmissbildung als eine mögliche teratogene Nebenwirkung des Anthelmintikums Piperazin? *Internist, 29,* 217-219.

Swedish Chemicals Inspectorate (2005) Piperazine. CAS No: 110-85-0, EINECS No: 203-808-3. Summary risk assessment report. Final report, 2005. European Commission. Institute for Health and Consumer Protection, European Chemicals Bureau (Special Publication I.05.72). URL: http://ecb.jrc.ec.europa.eu/documents/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/piperazinesum324.pdf

Wood, E. and Brooks, P.N. (1994) Piperazine hydrochloride: Dietary two generation reproduction study in the rat. Report to Akzo Nobel from Safepharm Laboratories Ltd., Derby. (unpublished).

AMP:

Chemical Ingredient Review (1990) Final report on the safety assessment of aminomethylpropanol and aminomethylpropanediol. *J. Am. Coll. Toxicol., 9*, 203-228.

Dow Chemical Company (2006) Amino alcohol: HPV Challenge Program, test plan for Tris(hydroxymethyl)aminomethane (77-86-1). Submitted to the U.S.E.P.A. under the High Production Volume (HPV) Chemicals Challenge Program. Midland, Mich.
URL: http://www.epa.gov/oppt/chemrtk/pubs/summaries/2amino2h/c16455tp.pdf

Internatioanl Programme on Chemical safety (2005) Isobutanolamine 2002. IPCS/CEC. URL: http://www.inchem.org/documents/icsc/icsc/eics0285.htm

IUCLID(2000) 2-amino-2-methylpropanol (124-68-5). European Chemical Substances Inform.
URL: http://ecb.jrc.ec.europa.eu/iuclid-datasheet/124685.pdf

Saghir, S.A., Clark, A.J., McClymont, E.L., Staley, J.L. (2008) Pharmacokinetics of aminomethylpropanol in rats following oral and a novel dermal study design. *Food Chem. Toxicol., 46,* 678-87.

MDEA:

Ballantyne, B. and Leung, H.W. (1996) Acute toxicity and primary irritancy of alkylalkanolamines. *Vet. Hum. Toxicol., 38,* 422-426.

Blaszcak, D.L. (1994) Guinea pig maximization test with *N*-methyldiethanolamine. East Millstone, N.J., Pharmaco LSR (Report 94-0991). Cited by Leung et al. (1996).

Geier, J., Lessman, H., Frosch, P.J., Pirker, C., Koch, P., Aschoff, R., Richter, G., Becker, D., Eckert, C., Uter, W., Schnuch, A. and Fuch, T. (2003) Patch testing with components of water-based metalworking fluids. *Contact Dermatitis, 49, 85-90.*

Henriks-Eckerman, M.L., Suuronen, K., Jolanki, R., Riala, R. And Tuomi, T. (2007) Determination of occupational exposure to alkanolamines inmetal-working fluids. *Ann. Occup. Hyg., 51,* 153-160.

Leung, H.W., Ballantyne, B. and Frantz, S.W. (1996) Pharmacokinetics of N-Methyldiethanolamine Following Acute Cutaneous and Intravenous Dosing in the Rat. *J. Toxicol.-Cutan. Ocul. Toxicol., 15*, 343-353.

Leung, H.W. and Blaszcak, B.S. (1998) Skin sensitization potential of four alkylalkanolamines. *Vet. Hum. Toxicol., 40*, 65-67.

Leung, H.W. and Ballantyne, B. (1997) Evaluation of the genotoxic potential of alkylalkanolamines. *Mutat. Res.-Genet. Toxicol. Environ., 393*, 7-15.

Werley, M.S., Ballantyne, B., Leung, H.W., Hermansky, S.K. and Fowler, E.H. (1997) Acute and subchronic repeated cutaneous application ofN-metyldiethanolamine in the Fisher 344 rat. *J. Toxicol.-Cutan. Ocul. Toxicol., 16,* 157-171.

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AUTHOR(S) Marit Låg, Åshild Andreassen, Christine Instanes and Birgitte Lindeman	CLASSIFICATION * A
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ABSTRACT

The toxicity studies of the amines, MEA, piperazine, AMP and MDEA, together with relevant groups of degradation products, nitrosamines, nitramines, aldehydes and amides, have been evaluated. However, the toxicological data are generally sparse. The amines, and the degradation products aldehydes and amides, seem to be irritative, piperazine is also reported to be sensitizing. For piperazine and MEA there are indications of reproductive and developmental toxicity. The aldehydes; formamide and acetamide, have in experimental animals induced developmental toxicity and carcinogenicity, respectively. Based on experimental data some nitrosamines are extremely potent carcinogens. Several of the nitramines are mutagenic and carcinogenic in rodents, although they seem considerably less potent than the corresponding nitrosamines.

The suggested exposure guidelines for the amines are based on the available literature. Particularly for AMP and MDEA there are few high quality studies. We suggest that the general population, over time, should not be exposed to levels in the air higher than 10 µg/m^3 MEA, 5 µg/m^3 piperazine base, 6 µg/m^3 AMP or 120 µg/m^3 MDEA. These values should be used as an indication and not as limit values for safety. Furthermore, it is desirable to reduce the human exposure of nitrosamines to an absolute minimum. Due to the serious effects of nitramines, exposure should also be kept at a low level. The irritating potential of the amines, aldehydes and amides may be the most relevant adverse health effect. Therefore, all these compounds have to be evaluated together with respect to irritating potential of the air around the gas plants.

NORWEGIAN TITLE

Helseeffekter av forskjellige aminer som er relevante for CO_2-fangst.

KEYWORDS		
CO_2 capture	Amines	Human toxicology

ABSTRACT (in Norwegian)

Toksikologiske studier av aminene, MEA, piperazin, AMP and MDEA, samt relevante grupper av nedbrytningsprodukter, nitrosaminer, nitraminer, aldehyder and amider, er gjennomgått i denne rapporten. Det mangler imidlertid mye kunnskap om de fleste av disse stoffene. Aminene, aldehyder og amider har irritasjonseffekter, og piperazin er også rapportert å være sensibiliserende. Videre er det indikasjoner på at piperazin and MEA kan gi reproduksjons- og utviklingsskader. Aldehydene, formamid and acetamid, kan gi henholdsvis utviklingsskader og være kreftfremkallende i forsøksdyr. Basert på eksperimentelle data synes noen nitrosaminer å være ekstremt kreftfremkallende. Flere nitraminer er også mutagene og karsinogene i gnagere, men de er mindre potente enn de tilsvarende nitrosaminer.

De foreslåtte retningslinjene for aminer er basert på tilgjenglig litteratur. Spesielt for AMP og MDEA er det få relevante og gode studier. Vi foreslår at den generelle befolkningen, over tid, ikke skal eksponeres for høyere nivåer i luften enn 10 µg/m^3 MEA, 5 µg/m^3 piperazin base, 6 µg/m^3 AMP eller 120 µg/m^3 MDEA. Disse verdier er en veiledning og ikke ment som grenseverdi for helseeffekter. Det er ønskelig å holde befolkningens eksponering for nitrosaminer så lavt som mulig. Også eksponering for nitraminer bør holdes på et lavt nivå på grunn av mulige, alvorlige helseeffekter. De irriterende egenskapene til aminer, aldehyder and amider synes imidlertid å være de mest relevante helseskadelige effektene i forbindelse med utslipp fra gasskraftverk. Den totale forekomsten av slike forbindelser i lufta rundt gasskraftverkene bør vurderes samlet.

** Classification* *A* *Unclassified (can be ordered from*
B *NILU)*
C *Restricted distribution*
Classified (not to be distributed)