INFOTOX (Pty) Ltd

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Retrieval and scientific interpretation of ecotoxicological information

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Toxicological Review for Monomethylamine

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1 Introduction and terms of reference

Sasol Group Services (Pty) Ltd ("Sasol") appointed INFOTOX (Pty) Ltd ("INFOTOX") to conduct desktop reviews of data available (particularly locally for the Highveld and Vaal Triangle areas) that relate air quality parameters to adverse health effects. The intention is to review a number of air pollutants and to eventually rank the pollutants in terms of adverse health impacts. There is also a requirement to review publicly available health studies on domestic fuel burning to quantify relative impact, which will be attended to in future reports, where relevant.

This INFOTOX report is the second report in Phase 1 of the study and presents a toxicological review for monomethylamine (MMA).

2 Chemical description

Alkylamines are colourless, flammable gases or liquids that emit "fishy" or ammonia-like odours. The alkylamines share common properties, including fat solubility, high alkalinity, and, for those amines with boiling points less than 100 °C (Table 4-1), considerable volatility. These properties account for their irritation to skin and mucous membranes and for their classification as hazardous chemicals in the workplace. General chemical properties of MMA are listed below (USEPA 2008 and HSDB online):

Chemical Abstracts Number	74-89-5
Molecular weight	31.06 g/mol
Boiling point	-6.3 °C
Density in air	1.07 (20 °C, versus air)
Conversion factor	1 ppm = 1.27 mg/m^3 at 20 ºC
Water solubility	1.25 x 10^6 mg/litre at 25°C

Vapours of MMA are heavier than air and may collect in low-lying areas. Under normal conditions, methylamine is a flammable colourless gas. At high concentrations, it has a pungent, acrid smell (SEPA online). MMA appears on the list of chemicals regulated under Section 112(r) of the US Clean Air Act as a flammable chemical. Section 112(r) of the 1990 Clean Air Act Amendments requires risk management planning and accidental release prevention for listed chemicals.

3 Occurrence in the environment

Methylamine is widely used in the chemical industry, but is also produced naturally by some plants, is found in animal urine and is released when animal or plant matter decays. Methylamine is not accumulated in the environment (SEPA online).

4 Overview of health effects

4.1 Carcinogenicity

Di- and trimethylamines are precursors of N-nitrosamines, which can act as potent carcinogens. It has been shown that fish contains methylamines and that consumption of fish increases

urinary excretion of methylamines in humans, but this source of methylamine exposure is not associated with increased cancer risks (Zeisel and DaCosta 1986). The 2008 review of the USEPA failed to identify studies of the carcinogenic potential of MMA in animals, and an updated INFOTOX literature search conducted for this report also did not find such studies. The International Agency for Research on Cancer (IARC online) and the USEPA (IRIS online) have not designated methylamine in terms of its carcinogenicity. It is the opinion of SEPA (online) that exposure to methylamine at normal background levels is unlikely to have any adverse effect on human health. Mixed results were seen in genotoxicity studies, in that mutagenicity was not seen in microbe-based test protocols with or without metabolic activation, but a positive mutagenic response was observed in the mouse lymphoma cell forward mutation assay, done in the absence of exogenous metabolic activation (reviewed in USEPA 2008 and in Hampton 2006).

4.2 Noncancer toxicity – acute exposures

The 2008 review of the USEPA failed to identify quantitative human acute MMA exposure studies, and an updated INFOTOX literature search conducted for this report also did not find such studies. In general, inhalation of air containing high levels of methylamine can result in a number of adverse health effects such as breathing difficulties, burning sensation, sore throat, headache and accumulation of fluid in the lungs (pulmonary oedema). Ingestion of high levels of methylamine can cause burns to the oesophagus and throat, a burning sensation and abdominal pain. Dermal contact with methylamine can cause severe skin irritation and burns. Contact with the eyes may cause severe burns and blurred vision (SEPA online).

Yang et al. (1995, cited by USEPA 2008) described the clinical care and treatment of residents of a community accidentally exposed to MMA vapour leaking from an overturned truck carrying liquid MMA. The exposure concentration and duration was unknown, but the duration was estimated at not more than a few hours. Persons requiring medical attention all had varying degrees of respiratory toxicity and chemical burns that led to oedema and tissue damage of the nose, mouth and lungs. Many also had lesions of the eyes and painful burns on exposed skin. Neurological effects included coma, fainting, dizziness, headache, nausea, vomiting and seizures.

Animal studies have shown MMA-induced toxicity to the liver, brain, and hematopoietic and nervous systems (USEPA 2008). During an exposure period of 40 minutes, the observed threshold of respiratory irritation was 129.5 mg/m^3 in rabbits (Izmerov et al. 1982 and Gorbachev 1957, cited in USEPA 2008).

Neurotoxicity is commonly described in animal toxicity studies at high concentrations at or close to lethality. Koch et al. (1980, cited in USEPA 2008) reported neurotoxic signs with respiratory and ocular irritation and lesions in rats exposed for 4 hours to 2 369 to 13 296 mg/m^3. The concentrations were sufficiently high to result in the death of some animals. In survivors, the neurotoxic symptoms persisted for 8 to 14 days after exposure. In the lower acute concentration range, Gorbachev (1957, cited in USEPA 2008) reported that neurobehavioral function in rats was disrupted by exposure to 50 mg/m^3 for 40 minutes.

4.3 Noncancer toxicity – subchronic and chronic exposures

The rat inhalation study by Kinney et al. (1990) is regarded as “well-conducted” (USEPA 2008). It was a repeat exposure study spanning two weeks and applied air concentrations in the

"lower" range, even though the lowest exposure concentration was still higher than the Level of Distinct Odour Awareness (LOA) of 0.71 mg/m^3 by at least one order of magnitude (see Section 5.1 for an explanation of the LOA). The lowest tested concentration was 95.3 mg/m^3, applied for 6 hours per day, 5 days per week, for 2 weeks (17.0 mg/m^3 when adjusted for continuous exposure). "*Only a mild irritation of the nasal turbinate mucosa"* was observed at the end of the exposure period. Since the effects are mild irritation only, the USEPA (2008) regarded this concentration as "*essentially a no-observed-adverse-effect-level (NOAEL)*".

The second-lowest applied concentration (Kinney et al. 1990) was 317.5 mg/m^3, at which the nasal mucosa was the primary target, showing lesions consisting of focal erosions and/or ulcerations, degeneration and/or necrosis. However, after a two-week recovery period, the lesions had completely dissipated and were not observable. At increasingly higher concentrations, effects with increasing severity were noted, but these concentrations are not of interest for the ambient exposure scenario that is the focus of the current review, and are not elaborated in this report. Similar findings of severe effects at higher concentrations, generally at shorter exposure periods, were summarised by the USEPA (2008), but are not of interest for the current review.

Dabaev (1981, cited in USEPA 2008), conducted a six month inhalation study on rats and described adverse effects on the nervous system, decreased levels of erythrocytes and decreased activity of some blood enzymes. Neurological effects occurred early in the exposure period, and the time of first observation was dose-dependent, with the earliest observations (within the second test week) reported in the highest dose group (0.271 mg/m^3). Neurological changes were not observed in the lowest dose group (0.004 mg/m^3). Adverse histopathological changes were seen in the liver, kidneys, lungs and heart, but not in the lowest dose group. Considering the results, 0.004 mg/m^3 is identified as a NOAEL.

MMA is metabolised in mammals by semicarbazide-sensitive amine oxidase (SSAO), and SSAO activity is greater in human than rodent tissues. Elevated levels of endogenous MMA and/or increased SSAO activity, and the resultant increased levels of the MMA metabolites, are believed to cause vascular endothelial damage, and are associated with a number of disease states such as diabetes, heart disease, Alzheimer's disease and inflammatory liver disease. Individuals with increased SSAO activity may therefore be a sensitive sub-population (Lewinsohn et al. 1978; Boomsma et al. 2000, cited in USEPA 2008).

4.4 Reproductive and developmental effects

A developmental study in mouse embryo cell cultures showed that monomethylamine was the least toxic compared with di- and trimethylamine, although all three types affected embryo development and survival (Guest et al. 1991, cited in USEPA 2008). Guest and co-workers also reported an in vivo study showing reproductive toxicity (decreased foetal body weights) associated with intraperitoneal injection, but this route of exposure was not considered for the current review.

Dabaev (1981, cited in USEPA 2008) reported male and female reproductive effects and developmental toxicity in a rat inhalation study for 6 months at 0.010 to 0.271 mg/m^3. The NOAEL for reproductive effects in this study was 0.004 mg/m^3.

5 Monomethylamine odour and health concerns

5.1 Odour and sensory perception

The sensory perception of odorous substances has four major components, namely, detectability, intensity, character and hedonic tone (Cha 1991).

Two types of thresholds are distinguished. Firstly, the odour detection threshold is the lower limit of the perceived odour intensity range that can be detected. It refers to the minimum concentration of a substance that would elicit a sensory response in the olfactory receptors of a specified percentage of a given population, usually 50 percent of the cases where the odour is present. Secondly, the odour recognition threshold refers to the lowest concentration at which the sensory effect can be recognised correctly in 50 per cent of the cases in the test group.

The USEPA (2008) calculated a Level of Distinct Odour Awareness (LOA) of 0.71 mg/m^3 for MMA based on the odor threshold of 0.044 mg/m^3 provided by Ruijten (2005). The LOA is defined by Van Doorn et al. (2002) as the concentration above which more than 50 per cent of the exposed population will experience at least a distinct odour intensity, and about 10 per cent of the population will experience a strong odour intensity.

The third characteristic of odour is described as its character, namely, its characteristic smell. The odour of MMA is described as an *"offensive fishy"* odour.

The fourth dimension of odour is its hedonic tone. This is a categorical judgement of the relative pleasantness or unpleasantness of the odour. Perception of hedonic tone is influenced by such factors as subjective experience, frequency of occurrence, odour character, intensity and duration. These factors determine when a specific odour becomes a nuisance to an individual. The nuisance threshold is defined as the concentration at which not more than a small percentage of the affected population (not more than 5 per cent) experiences annoyance for a small part of the time (less than 2 per cent). Because odour annoyance is influenced by a number of socio-economic psychological factors, WHO (2003) advised that a nuisance threshold cannot be determined on the basis of concentration alone.

The terminology described above is not followed consistently in the literature. Willhite and Dydek (1991) pointed out that widely variable odour thresholds are probably the result of variances in the test protocol, consideration of a single compound at a time as opposed to mixtures of contaminants in ambient air, the relationship between a laboratory-derived threshold and practical community odour perception, etc. These authors developed a guideline for predicting off-site odour impacts of sources from an odour impact model study that reported relationships between detection thresholds and complaint levels. It was indicated that compounds with an unpleasant odour have the potential to cause annoyance at concentrations exceeding three-times the detection threshold. Applying this 3-fold multiplier to the LOA of 0.71 mg/m^3 results in an estimated annoyance threshold of 2.13 mg/m^3 for MMA.

More recently, Collins and Lewis (2000) reviewed several studies that have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odours. The geometric mean of the ratios determined in these studies was a ratio of 5. According to these studies an unpleasant odour should result in annoying discomfort when it reaches an average concentration of 5 times its detection threshold. Applying the 5-fold

multiplier to the LOA of 0.71 mg/m^3 results in an estimated annoyance threshold of 3.55 mg/m^3 for MMA.

5.2 Description of symptoms at lower exposure levels

There is a paucity of toxicity studies of exposure in the region of the odour threshold. The studies by Kinney et al. (1990) were well-conducted, and the exposure resulted in "*only a mild irritation of the nasal turbinate mucosa"* at 17.0 mg/m^3 (adjusted for continuous exposure) regarded as "*essentially a NOAEL*". This concentration was higher than the LOA of 0.71 mg/m^3 by at least one order of magnitude. The study by Dabaev (1981) identified a NOAEL of 0.004 mg/m^3 for neurological, histopathological and reproductive effects, with effects reported at concentrations of 0.010 to 0.271 mg/m^3.

6 Summary of concentrations and effects of exposure to MMA

Table 6.1 lists ambient air concentrations of MMA selected from the literature review presented in this documented. Where available, averaging times are listed and the most pertinent observations are presented.

Table 6.1: Selection of concentrations for exposure to MMA in ambient air and key observations.

Concentration (mg/m^3)	Averaging time	Test specie(s)	Observation/endpoint/symptom	Reference(s)
0.004	6 months	Rat	NOAEL, considering neurological, reproductive and multiple organ effects	Dabaev 1981
0.71	Not specified	Human	LOA*	USEPA 2008
2.13 to 3.55	Not specified	Human	Estimated odour annoyance thresholds	INFOTOX**
17.0	Adjusted continuous exposure for 2 weeks	Rat	Mild irritation of nasal mucosa, essentially a NOAEL	Kinney et al. 1990 and USEPA 2008
50	40 minutes	Rat	Disrupted neurobehavioral function	Gorbachev 1957
129.5	40 minutes	Rabbit	Threshold of respiratory irritation	Izmerov et al. 1982 and Gorbachev 1957

*LOA: Level of Distinct Odour Awareness. The concentration above which more than 50 per cent of the exposed population will experience at least a distinct odor intensity, and about 10 per cent of the population will experience a strong odour intensity (defined by Van Doorn et al. 2002).

** Estimated by INFOTOX from the LOA derived by the USEPA (2008), using estimation methods suggested by Willhite and Dydek (1991) and Collins and Lewis (2000).

The intention of this table is to provide a framework for the health-risk based interpretation of ambient air concentrations recorded in the Sasol study area. The exposure concentrations and health observations in the table have been collated from a review of the scientific literature, as presented in the preceding sections.

7 Discussion and conclusions

Table 6.1 summarises the available concentration-response data for MMA and is a good reflection of the general lack of toxicological data to date. The estimated concentrations that might give rise to odour annoyance are known, and can be practically applied to manage emissions in order to avoid complaints by potentially exposed communities.

The available toxicology and epidemiology database is not robust and characterised by very few available studies. Strictly following the definition of exposure periods of the Agency for Toxic Substances and Disease Registry (ATSDR online), the Kinney et al. (1990) study covered the acute exposure period. This 2-week laboratory animal study was judged of good quality and was the only study with quantitative data available for acute exposure. The longer 6-month subchronic study by Dabaev (1981) was conducted at lower concentrations, but the quality of this study was not discussed in detail by the USEPA, which included the study in the literature review for the USEPA (2008) report. Unfortunately, the original Dabaev report is in Russian, therefore the quality cannot be easily ascertained. Chronic exposure studies were not available at all.

It is concluded that the NOAEL of 17.0 mg/m^3 derived from the Kinney et al. (1990) study is suitable for application to acute (up to and including 14 days) periods of exposure to monomethylamine. The availability of a single study cannot be regarded as a strong database for the derivation of an acute guideline concentration, but is all that is currently available. Applying an uncertainty factor of 10 for inter-species variation and 10 for intra-species sensitivity, results in an acute guideline concentration of 0.170 mg/m^3. An additional uncertainty factor was not applied for the limitations in the database, because the NOAEL was based on mild effects and the available study was judged of good quality.

Regarding the chronic exposure period, it was concluded that the available study by Dabaev (1981) is not sufficiently dependable for the derivation of a subchronic guideline concentration. A chronic exposure guideline can also not be derived, since chronic exposure studies were not available at all.

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