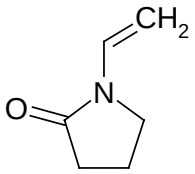
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-12-0
Chemical Name	1-Vinyl-2-pyrrolidone
Structural Formula	

RECOMMENDATIONS

The chemical is currently a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-vinyl-2-pyrrolidone (NVP) is rapidly and extensively absorbed following inhalation and ingestion and its physicochemical properties suggest that it will readily cross the skin. Readily formed metabolites of NVP are eliminated within 24 hours after dosing, predominantly in the urine. There is no evidence that NVP is retained in any tissue and it has been shown that NVP and its metabolites do not bind to plasma proteins or DNA to any great extent.

Toxicity occurs in animals following a single exposure by inhalation, ingestion or in contact with the skin. The liver and kidneys have been identified as target organs by all three routes of exposure and following oral or inhalation exposure, irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs. A 4-hour LC_{50} of 3070 $mg.m^{-3}$ for aerosols of NVP has been identified in the rat. However, 6-8 hour exposures to saturated vapour (about 600 $mg.m^{-3}$) in a range of species produced some local irritation but no deaths. It is not clear why the signs of toxicity were less severe in the vapour experiments, although localised deposition of liquid NVP in the aerosol study may have increased the severity of reactions. No effects were observed in rats or mice inhaling 23 $mg.m^{-3}$ NVP vapour for 6 hours on 2 consecutive days, though slight liver toxicity was evident in rats immediately after 2 six-hour exposures to 69 $mg.m^{-3}$ NVP vapour. Oral LD_{50} values are around 1000 mg/kg for the rat and mouse. A dermal LD_{50} of 560 mg/kg has been reported for rabbits and deaths among rats administered around 1000 mg/kg on the skin indicate that the LD_{50} value may lie below 2000 mg/kg for this species.

NVP is not a skin irritant but in liquid form is a severe eye irritant. NVP has the potential to cause respiratory tract irritation based on observations of increased respiration rates and inflammation in nasal mucosa membranes in inhalation toxicity studies and the knowledge that NVP is severely irritating to the eye. NVP does not cause skin sensitisation and does not bind to proteins to any great extent. NVP would not be predicted to cause respiratory sensitisation, at least not by an immunological mechanism.

Repeated inhalation of NVP by rats and mice resulted in dysproteinaemia, haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx. In the liver, centrilobular hepatocyte necrobiosis and fatty infiltration accompanied by degenerative changes in the nucleus. In the nasal cavity, NVP caused inflammatory changes in the olfactory and respiratory epithelia and larynx. A NOAEL of 1 ppm (4.61

mg.m$^{-3)}$ has been identified in a 3 month study in the rat. In rats inhaling 5 ppm (23 mg.m^{-3}) NVP vapour for 3 months observations included clear evidence of nasal cavity irritation and slight dysproteinaemia. Although no histopathological changes were found in the livers of rats exposed to 5 ppm NVP for 3 months, liver toxicity became more marked when rats inhaled 5 ppm for longer durations. This suggests that NOAELs derived from 3-month studies might not apply to studies of longer duration and the lifetime exposure NOAEL might be below 1 ppm for rats and mice. Inhalation of concentrations of 15 ppm (69 mg.m^{-3}) NVP vapour or more resulted in liver toxicity and nasal cavity irritation within 1 week and mortality occurred at concentrations of 45 ppm (207 mg.m^{-3}) in mice and 120 ppm (553 mg.m^{-3}) in rats.

In contrast, when NVP is given by oral gavage to rats, the dose levels required to induce histopathological changes in the liver are considerably greater than those required by inhalation; the respiratory tract is not a target tissue with oral dosing. One explanation for the much lower systemic toxicity of NVP by the oral route is that the substance hydrolyses in the acidity of the stomach prior to absorption. A NOAEL of 3.6 mg/kg/day has been identified in a drinking water study. However, gavage doses of up to 60 mg/kg/day produced no clear pathological changes in the liver and only slight changes in a few biochemical and haematological parameters. There are no data relating to the effects of repeated dermal exposure to NVP.

NVP has yielded consistently negative results in genotoxicity tests in a wide variety of *in vitro* systems, and one well conducted *in vivo* test covering the endpoints of gene mutation, chromosomal aberration and DNA-binding. On this basis, it can be concluded that NVP is not a genotoxicant.

NVP vapour is clearly carcinogenic in rats, the only species tested. In a 2 year inhalation study, hepatocellular carcinoma, nasal cavity adenomas and adenocarcinomas, and squamous cell carcinomas in the larynx were observed. In another study, irreversible changes were produced in the liver of rats after only 3 months exposure, which resulted in liver tumour development at the end of a subsequent 21 month observation period in the absence of further exposure to NVP. This suggests that these tumours, and possibly also nasal and laryngeal tumours, arise by a process involving more than simply chronic tissue damage/inflammation. Overall, it is unclear what toxicological mechanism underlies the formation of NVP vapour-induced tumours and it is also unclear where a no-effect level lies. Given these uncertainties, and in the absence of evidence to the contrary, it is suspected that these tumours are of relevance for human health. The carcinogenicity of NVP by the oral and dermal routes has not been studied.

Fertility has not been specifically investigated. However, in repeated dosing studies NVP showed no adverse effects on the reproductive organs of rats and mice inhaling up to 45 ppm for 3 months, rats inhaling up to 20 ppm for 2 years and given up to 8.3 mg/kg NVP in drinking water for 3 months. On this basis it is considered that there is no evidence to suggest that NVP is likely to have an adverse effect on fertility. No further studies are required in the OECD SIDS programme.

In a developmental toxicity study in rats exposed by inhalation, foetotoxicity, consistent with delayed development, was seen at exposure concentrations producing significant maternal toxicity (20 ppm). No specific malformations or foetotoxicity was observed at concentrations that were not also maternally toxic. A NOAEL of 1 ppm (4.61 mg.m^{-3}) was indicated for maternal toxicity, with a NOAEL of 5 ppm (23 mg.m^{-3}) for effects on the foetus. In addition, there was some evidence that pregnant rats may be more susceptible to the toxicity of NVP than non-pregnant rats

Environment

The environmental effects database meets the requirements of the SIDS data package. The substance shows moderate to low toxicity to aquatic organisms in short-term tests. *Daphnia magna* was the most sensitive species tested, with a 48 hour EC_{50} of 45 mg/l. A predicted no effect concentration (PNEC) of 45 µg/l for surface water was derived from this value using an assessment factor of 1,000. A PNEC*microorganisms* for waste water treatment processes was estimated to be 19.95 mg/l based on an assessment factor of 100 on a threshold concentration of >1995 mg/l for effects on activated sludge respiration. PNECs for sediment and soil were estimated using the equilibrium partitioning method as PNEC*sediment* = 51.8 µg/kg wet wt. and PNEC*soil* = 18.7 µg/kg wet wt.

No data are available to allow a PNEC to be derived for the atmospheric compartment. However, the atmospheric concentrations of 1-vinyl-2-pyrrolidone are predicted to be very small and so adverse effects are unlikely.

Exposure

In 1999, there was understood to be only two producers of 1-Vinyl-2-pyrrolidone (NVP) worldwide in the EU and in the USA. The annual production volume in 1999 was 10-50 000 tonnes.

The majority of the NVP that is sold within the EU is used in the production of polyvinyl pyrrolidone or copolymers. According to manufacturers, the amount of residual monomer is less than 1000 ppm. Polyvinyl pyrrolidone has a range of uses, including in pharmaceuticals, cosmetics and food additives. Copolymers of NVP are used as viscosity improvers in oils and in water-borne paints and adhesives. 1-Vinyl-2-pyrrolidone is also used as a reactive thinner to produce copolymers in UV-cured inks and coatings. Radiation-curable inks contain up to 14% NVP and are used, for example, in advertising hoardings. Radiation-curable coatings and varnishes have a number of uses, including coating printed circuit boards, and on children's toys, and contain up to 9% of NVP. In all these cases there is only a very small amount of residual monomer (NVP) left in the finished product.

1-Vinyl-2-pyrrolidone is a liquid at room temperature with a melting point of 13-14^{o}C, a boiling point of 90-92^{o}C, a vapour pressure of 0.12 hPa at 20^{o}C. It is fully miscible with water and has a measured Log n-octanol water partition coefficient (log Kow) of 0.4.

Environmental releases can occur to the atmosphere and wastewater streams during production of NVP, polymer manufacture and processing, formulation of radiation-cured coatings and inks and via in-service losses of residual NVP-monomer during use of polymer products.

The substance is readily biodegradable and so is expected to biodegrade in water, soil and sediments under aerobic conditions. It is also expected to be rapidly degraded in the atmosphere by reaction with hydroxyl radicals and a half-life for this reaction of around 10.4 hours has been estimated. The rate constant for the reaction of NVP with hydroxyl radicals in aqueous solution has been measured and is 7.3 10^{9} l/mol·sec.

The substance has a low Henry's law constant (0.0056 Pa m^3 mol^{-1}) and so is not expected to volatilise rapidly from water. The low log Kow value indicates that the substance a low potential for adsorption onto soil, sediment or suspended matter, and a low potential for bioaccumulation. The organic carbon-water partition coefficient (Koc) has been estimated as 16.9. Based on the physicochemical properties, NVP would be expected to partition to water.

The manufacture and polymerisation of NVP is carried out in closed systems. Exposure by both the inhalation and dermal routes may occur during deliberate breaches of the system. The main sources of exposure from the manufacture of UV curing inks and lacquers are thought to arise during the charging of mixing vessels and during the filling of product containers and from incidental dermal contact with contaminated surfaces. The main source of exposure to NVP during the manufacture of contact lenses is during the preparation of the pre-polymer mix and when this mix is put into the moulds. In consumers, there is potential for inhalation exposure from the use of hairspray containing residual NVP monomer. There is very low potential for exposure from ingestion or contact with the skin to of residual NVP monomer in polyvinylpyrrolidone (PVP) used in consumer products. Individuals may also be exposed at a low level to NVP monomer indirectly via the environment from dietary sources such as drinking water, fish, leaf and root crops, meat and milk but NVP may also be inhaled.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and other non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

National or regional exposure gathering information, and if indicated risk assessment, may need to be considered.

A regional risk assessment has been carried out for Europe. As it was not possible to identify a NOAEL for carcinogenicity seen in rodents there were particular concerns for workers (with or without exposure to NVP from

the environment and/or consumer products) involved in the production of NVP and its use in the production of polymers, the use of NVP in the manufacture of UV curing inks/lacquers, the use of UV curing inks/lacquers containing NVP, and the use of NVP in the manufacture of contact lenses. In addition, there were concerns for single exposure toxicity and respiratory tract irritation in exposure situations where there is the potential for peak exposures to occur. Such peak exposures can occur during the production of NVP and its use in the production of polymers, the use of NVP in the manufacture of UV curing inks/lacquers, the use of UV curing inks containing NVP. It was recommended that steps should be taken to reduce exposures for these occupational uses. It was also recommended that steps should be taken to prevent eye contact with liquid NVP in any situation where this may occur. No concerns were identified for workers whose only form of exposure to NVP was as a residue in NVP based polymers owing to the very low level of NVP to which these workers would be exposed. For consumers and exposures from the environment there was no need for further information and/or testing or for risk reduction measures beyond those which are being applied already. As exposures were so low, there were no concerns for all environmental compartments for production, processing and use of NVP and release of NVP during use of polymers which contain residual NVP monomer.

A national risk assessment has been carried out in Australia. The occupational risk assessment concluded that a risk of acute eye effects is likely during formulation of NVP products and steps be taken to reduce exposure. There were concerns for workers involved in the formulation of NVP products and use of UV curing inks containing NVP. There were no concerns for the environmental compartments. The public health assessment concluded that it is prudent to limit the levels of NVP to below 200 ppm in PVP used in cosmetics as high consumer exposure is likely at levels greater than this level.