EUROPEAN COMMISSION
DIRECTORATE-GENERAL HEALTH AND CONSUMER PROTECTION
Directorate C - Scientific Opinions
Unit C2 – Management of Scientific Committees; scientific co-operation and networks

Scientific Committee on Toxicity, Ecotoxicity and the Environment

Brussels,
C2/JCD/csteeop/**1-V-2-PyrroHH07122001**/D(01)

SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on the results of the Risk Assessment of:

1-Vinyl-2-Pyrrolidone

CAS No.: 88-12-0
EINECS No.: 201-800-4

REPORT VERSION (Human Health)
September 2001

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

Opinion expressed at the 28th CSTEE plenary meeting

Brussels, 07 December 2001

[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94, which is supported by a technical guidance document.

Terms of reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report?

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

GENERAL COMMENTS

The assessment follows the recommendations of the TGD and is comprehensive and properly written. All relevant endpoints are addressed.

The CSTEE agrees in general with the overall conclusions of the risk assessment.

SPECIFIC COMMENTS

Exposure Assessment

The number of producers and users of N-VP in Europe is small and for confidentiality reasons no tonnage information has been included into the RAR. N-VP is mainly produced for the manufacture of polymers used in pharmaceuticals, adhesives, and cosmetics.

N-VP is a liquid that is produced in closed systems, most polymerisation processes are carried out on the same site as N-VP production. The main exposure is during intermittent breaching of the systems or from fugitive emissions. Therefore, the main routes to consider are the inhalation and dermal routes.

Most occupational exposures are below 0.1 ppm (8-hr TWA), but exposures were up to 5 ppm for the manufacture of UV curing inks and lacquers (EASE estimate), and up to 7-14 ppm for manual screen printing (EASE).

Consumer exposure to residual N-VP in consumer products is considered to be negligible.

Human exposure indirectly via the environment is very low and estimated to range up to 4 μg/kg/d with inhalation from production and dietary sources contributing mostly to this exposure.

Effects assessment

N-VP is rapidly absorbed, and widely distributed throughout the body. It is metabolised to polar compounds that are mainly eliminated in the urine. N-VP exhibits acute toxicity by the

oral, inhalation and dermal routes. It is not irritating to the skin, but liquid N-VP is a severe eye irritant. Based on observations in inhalation studies a NOAEL for sensory irritation is assumed at around 15 ppm. N-VP is not sensitising to the skin and is not expected to act as a respiratory allergen.

Following repeated exposures by inhalation, disturbances of protein synthesis, hepatotoxicity and changes in the epithelium of the respiratory tract were found. No clear no-observed-adverse-effect level (NOAEL) could be established in mice. In rats, a lowest-observed-effect level (LOEL) of 5 ppm was found in a 12-months study. Studies with observations after recovery periods showed that three months exposure to doses ≥ 15 ppm induced hepatotoxic changes which subsequently progressed to neoplastic lesions.

Repeated dose studies by the oral route showed a NOAEL for rats of 3.6 mg/kg bw/d. Slightly reduced bodyweight gain and increased hepatic enzyme activity were detectable at dose levels between 40 and 60 mg/kg bw/d, but without clear pathological changes in the liver. No changes in the respiratory epithelium were seen.

N-VP was not found to be genotoxic. *In vitro,* several Ames tests were all negative both in the absence and in the presence of metabolic activation. N-VP was also tested negative in assays for gene mutations at the HPRT and TK locus in mouse lymphoma cells. No chromosomal aberrations were seen in human lymphocytes. N-VP did not induce unscheduled DNA synthesis in rat hepatocytes. In a poorly documented study, a slight increase in sister chromatid exchange (SCE) frequency in human lymphocytes was reported. However, the relevance of this finding is presently unclear. *In vivo*, a Drosophila sex-linked recessive lethal assay showed no indication of genotoxicity nor did N-VP induce micronuclei in a well performed gavage study in mice. No evidence of binding to DNA was found in liver cells from rats treated intraperitoneally with N-VP.

No relevant epidemiological data were available on the carcinogenic potential in humans.

N-VP was tested for carcinogenicity in Sprague-Dawley rats by the inhalation route and caused hepatocellular carcinomas, adenomas and adenocarcinomas of the nasal cavity and squamous cell carcinomas of the larynx in both sexes. A NOAEL could not be identified as tumours occurred at 5 ppm which was the lowest dose tested. It is notable that changes can be produced in the liver of rats after only 3 months exposure to N-VP, resulting in liver tumour development at the end of 2 years even in the absence of further N-VP exposure.

In a recent re-evaluation of N-VP, IARC (1999) concluded that there is limited evidence for the carcinogenicity of N-VP in experimental animals and that N-VP is not classifiable as to its carcinogenicity to humans (Group 3). This evaluation should be included into the RAR.

No fertility study has been performed. However, changes in the reproductive organs have not been detected in repeated dose studies and hence no adverse effects on fertility are anticipated.

In rats, an inhalation study on the developmental toxicity showed no adverse effects on the foetus except for some developmental retardation (reduced weight and retarded ossification) at maternally toxic doses (NOAEL, maternal toxicity: 1 ppm; NOAEL, foetotoxicity: 5 ppm).

Risk characterisation

There are no concerns regarding skin irritation, sensitisation, mutagenicity and fertility. The CSTEE agrees with the conclusion ii) for these endpoints for all occupational and consumer scenarios. Steps should be taken to prevent accidental eye contact with liquid N-VP.

The main adverse effects of concern are the nasal cavity, laryngeal and liver tumours that occur after repeated exposures to N-VP. It is unclear which toxicological process underlies the formation of N-VP induced tumours and it must therefore be assumed that these tumours are of relevance to humans. In addition, there are concerns for acute toxicity and respiratory tract irritation in situations where there is potential for peak exposure.

Since the LOAEL for pregnant rats in the developmental study was identical to the LOAEL for repeated dose toxicity (5 ppm), no separate risk characterisations had to be performed for the two endpoints and the same conclusions apply.

Workers

Most exposures are below 0.1 ppm (8-hr TWA), but can be up to 5 ppm for the manufacture of UV curing inks and lacquers, and up to 7-14 ppm for manual screen printing (EASE estimates). Hence, in some occupational scenarios (*i.e.* except those in which exposure is only to residual monomers) the predicted exposures are close to concentrations at which tumours have occurred in rats and, therefore, give rise to concern. In addition, dermal exposures of between 0.1 – 1 mg/cm²/d could occur with a corresponding additional body burden.

Peak exposures of up to 14 ppm, or possibly higher, may occur during maintenance and cleaning tasks and in the manufacture and use of UV curing inks. Since histopathological changes (though minimal) have been found in the livers of rats exposed to 15 ppm on two successive days, regular short-term exposures to high levels of N-VP might induce adverse effects, including respiratory tract irritation, and, therefore, also cause concern.

The CSTEE agrees with conclusion iii) for workers (except those in which exposure is only to residual monomers).

Consumers

The levels of residual N-VP in consumer products are so low (1-100 ppm) that here are no concerns for risks to human health. The worst case estimate for total daily exposure to N-VP from pharmaceuticals and consumer products was about 0.8 µg/kg bw (estimated intakes of residual N-VP from pharmaceuticals, denture fixative, cosmetics, washing powder and contact lenses, assuming 100% absorption by all routes). This is about 2000 times lower than the body burden that would arise in rats inhaling 5 ppm for 6 hours per day. The use of N-VP in hairspray may give rise to repeated inhalation exposure. The estimated exposure concentration to which a consumer could be exposed per event is 1.5×10^{-6} ppm. This is six orders of magnitude lower than the LOAEL in rats.

In its recent evaluation, the Scientific Committee for Food concluded that the intakes of N-VP from food additive uses of PVP and PVPP do not give cause for concern (SCF, 2001).

The CSTEE agrees with conclusion ii) for consumers.

Indirect Exposure via the Environment

The intake from both dietary sources and by inhalation via the environment is so low that there are no concerns for risks to human health. The CSTEE agrees with conclusion (ii).

References

IARC, 1999: Monographs on the evaluation of carcinogenic risks to humans, Vol. 71, p. 1181-7

SCF, 2001. Opinion of the Scientific Committee on Food on the Safety of N-Vinyl-2-Pyrrolidone in Polyvinylpyrrolidone and Polyvinylpolypyrrolidone (insoluble Polyvinylpyrrolidone) when used as food additives.