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Opinion of the Scientific Committee on Food on the safety of N-vinyl-2-pyrrolidone residues in polyvinylpyrrolidone and polyvinylpolypyrrolidone (insoluble polyvinylpyrrolidone) when used as food additives

(expressed on 30 May 2001, corrected on 17 April 2002)

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OPINION
OF THE SCIENTIFIC COMMITTEE ON FOOD
ON THE SAFETY OF N-VINYL-2-PYRROLIDONE RESIDUES IN POLYVINYLPYRROLIDONE AND POLYVINYLPOLYPYRROLIDONE (INSOLUBLE POLYVINYLPYRROLIDONE) WHEN USED AS FOOD ADDITIVES

(Adopted by the SCF on 30 May 2001, corrected on 17 April 2002)

Terms of Reference

The Scientific Committee on Food is requested by the Commission to evaluate the safety of the residues of N-vinyl-2-pyrrolidone (NVP) monomer, proposed at the level of 10 mg/kg in the specifications for the food additives polyvinylpyrrolidone (PVP) and polyvinylpolypyrrolidone (PVPP), taking into account their allowed uses and other exposure sources for NVP.

Background

NVP is used as a co-monomer of a thickening agent in adhesives for gluing paper and board for food packaging purposes. This use of NVP could give rise to migration of NVP into packaged food and this is the subject of a separate opinion by the Committee. During its consideration of the food packaging uses of NVP the Committee noted that the existing food additive specifications for PVP allow residues of the monomer NVP up to 1% (JECFA, 1986) and for PVPP (insoluble PVP) up to 0.1% (JECFA, 1988). The Committee also noted that toxicological data on NVP shows this substance to be a non-genotoxic carcinogen by inhalation in rats and to have other toxic effects in other laboratory animal species by various exposure routes (IARC, 1999). This prompted a re-evaluation of the food additive use of PVP and PVPP from the point of view of possible exposure to residues of NVP.

PVP and PVPP are currently permitted as excipients in tablets for tabletop sweeteners and dietary supplements, whilst PVPP is also permitted as a processing aid in the clarification of beer and wines (SCF, 1992). Consumers of food could thus be exposed potentially to the monomer through ingestion of these additives. Occupational exposure occurs industrially during the manufacture of NVP monomer and polymers, the manufacture and use of UV curing inks and lacquers, and plastic contact lenses. Potential consumer exposure to PVP and PVPP occurs also from their use in pharmaceuticals as tablet constituents, as ingredients in cosmetics and toiletries such as skin cleansers, antiseptic preparations containing iodine, mouthwashes, denture fixatives and eye drops, as washing powder additives and as paint dispersions (HSE, 2000).

PVP and PVPP themselves have been evaluated previously by JECFA, when PVP was allocated an ADI of 0-50 mg/kg b.w. (JECFA, 1987) and PVPP an ADI not specified (JECFA, 1983).

Toxicological data

A large number of toxicological investigations are available for NVP and have been summarised by the UK Health and Safety Executive (HSE, 2000). *In vitro* hydrolysis studies have demonstrated rapid hydrolysis at the acid pH of the mammalian stomach (half-life of 1.5

minutes at pH 1.2), the liberated acetaldehyde being rapidly oxidised to acetate by mitochondrial aldehyde dehydrogenase and cytosolic aldehyde oxidase and xanthine oxidase. However, hydrolysis was slower at higher pH (20-40 minutes at pH 2.2-2.5) and could be slower *in vivo* when food is present in the stomach. Oral toxicokinetic studies with ^{14}C-labelled NVP in rats showed rapid absorption of the radiolabel and wide distribution throughout the body tissues, the highest tissue levels appearing in the liver (10% as against <1% in most other tissues). Most of the radioactivity (about 75%) was excreted in the urine, about 0.4% appearing in the faeces, and about 1% being found as $^{14}CO_2$ (Digenis, 1990). There was considerable enterohepatic circulation (McClanahan et al., 1984). Inhalational toxicokinetic studies in dogs showed absorption from the respiratory tract but yielded no suitable quantitative data (BASF, 1992a). Metabolism studies using ^{14}C-labelled NVP showed the major metabolites, of which about 12% were acetic acid, to be highly polar, but the structures of the remainder were not identified (Digenis & McClanahan, 1982).

Acute oral, inhalational and dermal toxicities were determined in a variety of laboratory animals (HSE, 2000). Skin and eye irritation as well as sensitisation potential were also investigated (HSE, 2000).

Several short-term inhalational studies in mice, extending from 10 days to 6 months, did not establish a clear no-observed-effect level (NOEL) but showed as adverse effects disturbances of protein synthesis, mild hepatotoxic changes and proliferative changes in the epithelium of the respiratory tract.

A number of inhalational investigations using different strains of rats, most of which extended over 3 months and one over 12 months, showed similar signs of toxicity as seen in the mouse studies. In one of the 90-day rat studies a NOEL of 0.0046 mg/l, equivalent to 0.34 mg/kg b.w./day, was established (BASF, 1986b). In another 90-day study a lowest-observed-effect level (LOEL) of 0.023 mg/l, equivalent to 1.7 mg/kg b.w./day, caused only slight effects on protein production and slight changes in the nasal respiratory epithelium but no hepatotoxicity (BASF, 1986a). Studies which included observations after recovery periods showed that three months exposure to doses ≥ 0.069 mg/l (equivalent to 5.1 mg/kg b.w./day) induced irreversible hepatotoxic changes which subsequently progressed to neoplastic lesions (BASF, 1987d). Exposure to 0.023 mg/l for twelve months produced increased liver weight, spongiosis hepatis and foci of cellular alterations as well as inflammation and hyperplasia of the nasal and respiratory epithelium (Klimisch et al., 1997b). As more than 90-days of exposure was necessary to produce hepatotoxic effects at the LOEL of 0.023 mg/l the possibility has to be considered that even exposure to the NOEL of 0.0046 mg/l, if extended well beyond 3 months, might eventually also cause hepatotoxicity.

A 90-day inhalational study in Syrian hamsters exposed to 0.207 mg/l did not indicate any hepatotoxicity in this species but the liver was the only organ investigated (BASF, 1987e). Although inhalational studies were carried out also in cats, rabbits, and guinea-pigs no detailed results were obtainable for evaluation (BASF, 1964a, 1941).

Several oral studies in rats, extending from 28 - 90 days and using doses from 0.5 to 100 mg/kg b.w. via drinking water or by gavage, showed that adverse toxic effects such as slightly reduced bodyweight gain and increased γ-GT in hepatic cells were still detectable at dose levels down to 40 mg/kg b.w. but clear hepatotoxic effects only became noticeable at doses above 60 mg/kg b.w. At doses of 100 mg/kg b.w. small hepatic foci of morphological cellular alteration were seen but none stained positive for glycogen or γ-GT. No changes in the respiratory epithelium were seen at any dose (BASF, 1986c). The NOEL in these studies was

3.6 mg/kg b.w. and the LOEL of 8.3 mg/kg b.w. produced only disturbances in protein production (BASF, 1986d). These results clearly show a route-dependent difference in toxicity, probably as a consequence of the ready hydrolysis of NVP in the acid environment of the stomach.

Gavage studies were also carried out in rabbits, cats and guinea-pigs but as they lacked control groups, the results were not considered to add any useful toxicological information (BASF, 1964b).

No oral or dermal long-term studies were carried out. The only available chronic toxicity study is an inhalational study with 99.9% pure NVP in Sprague-Dawley rats extending over 2 years. Doses ranged from 0.023-0.092 mg/l (1.7-6.8 mg/kg b.w.). The adverse effects noted were dose-related and similar to those seen in the short-term studies i.e. reduced body weight gain, disturbed protein production, biochemical and organ weight changes suggestive of hepatotoxicity, such as focal hyperplasia, foci of cellular alteration, spongiosis hepatis, and focal hyperplasia and inflammation of the respiratory epithelium. In addition, there were dose-related increases in hepatocellular carcinomas in males and females as well as in adenomas and adenocarcinomas of the nasal epithelium and squamous cell carcinomas of the larynx in males and females exposed to the highest doses of NVP. A clear NOEL was not identified (Klimisch et al., 1997a). In a recent re-evaluation of NVP, IARC (1999) concluded that there is limited evidence for the carcinogenicity of NVP in experimental animals and that NVP is not classifiable as to its carcinogenicity to humans (Group 3).

No specific oral studies on reproductive performance have been conducted. The examination of reproductive organs in the rat oral gavage and the inhalational studies did not disclose any unusual findings. A developmental toxicity study in the rat by the inhalational route showed no adverse effects on the embryo and fetus except for some developmental delay (reduced fetal weight and retarded ossification) at a dose causing maternal toxicity (HSE, 2000).

The genotoxicity of NVP was examined in several *in vitro* studies in bacterial systems. In these tests NVP was found to be not mutagenic (HRC, 1978c; BASF, 1978b; Simmon and Baden, 1980; Knaap et al., 1985). Various *in vitro* tests in cultured mammalian cells, including the use of closed systems, also indicated the absence of any mutagenic potential. These comprised assays for chromosomal aberrations in human lymphocytes (BASF, 1987f), assays for gene mutations at the HPRT and TK locus in mouse lymphoma L5178Y cells (Litton Bionetics, 1980a; Knaap et al., 1985), an assay for unscheduled DNA synthesis in rat hepatocytes (Litton Bionetics, 1980b), assays for the induction of sister chromatid exchanges in cultured lymphocytes (Norpa & Tursi, 1984) and for cell transformation in BALB/3T3 cells (Litton Bionetics, 1980c). *In vivo* tests with negative outcome included a sex-linked recessive lethal test in *Drosophila melanogaster* (Knaap et al., 1985) and a micronucleus test in NMRI mice (BASF, 1993b). NVP was thus found to be non-genotoxic.

Intake considerations

The Committee understands from information recently submitted by the European industry, that PVP is not used in tabletop sweeteners but may be used in solvable and chewable dietary supplement tablets (European Federation of Health Products Manufacturers, 2000). The annual production of PVP and PVPP amounts to about 3500 tons of which some 2000 tons are used by the pharmaceutical industry, about 1000 tons are used for beer and wine clarification and about 200 tons are used for food supplements (CEFIC, 2000).

Estimates of the amount of PVP used in food supplements range from 5-31 g/kg food supplement, the typical amount being 25 g/kg. The average weight of a supplement tablet is estimated to be 1 g but some non-chewable tablets could weigh as much as 1.85 g (Council for Responsible Nutrition, 2000). As the presence of the monomer NVP in PVP and PVPP is limited to 10 ppm in the currently proposed specifications, consumption of 1 mg of either compound will contribute only 0.01 µg NVP to the total exposure of the consumer (BASF, 2000). The ingestion of a 1 g food supplement tablet thus represents an intake of 0.05-0.31 µg NVP equivalent for a 60 kg person to a daily dose of 0.0008-0.0052 µg NVP/kg b.w.

The maximum residue of NVP from the use of PVPP in the clarification of beer and wine is estimated at 5 µg/l of beverage, based on experimental technological data (Madigan et al., 2000; Chandra-Gopal et al., 2000; Gautier, 1995). Thus consumption of 2L of beer and wine/day may contribute an intake of up to 0.17 µg/kg b.w/day of NVP for a 60 kg person. The Committee understands, however, that the Community Code of Oenological Practice and Processes limits the maximum content of free NVP in PVPP to 0.1%, which exceeds the proposed specification limit for NVP in PVPP by about 100-fold and wishes to draw the attention of the Commission to this discrepancy (European Commission, 2000).

Surveys of potential daily exposure to NVP from occupational sources yielded estimates of total intakes ranging from 0.66-29.20 mg/kg b.w./day (HSE, 2000). The worst case estimate for total daily exposure to NVP from pharmaceuticals and consumer goods was about 2.1 µg/kg b.w. (HSE, 2000). The Committee notes that estimated intakes of residual NVP from food, beverages and supplement tablets are only a few nanograms and considers these quantities to be negligible compared with the intakes of NVP arising from dermal or inhalational exposures from occupational and non-food sources.

Conclusions

The Committee noted that there was a difference of 4-5 orders of magnitude between the estimated potential exposure through ingestion of NVP from food, beverages and food supplement tablets, and the tumorigenic dose for liver and respiratory epithelium found in rats exposed to NVP by the inhalational route. The Committee also noted that there was a considerable reduction in the toxic potency of NVP for the liver when administered by the oral route compared with inhalation and that NVP may be hydrolysed in the stomach. Although the mechanism of toxicity of NVP remains unknown, NVP does not appear to be genotoxic *in vitro* or *in vivo.* The Committee noted similarly that there was an adequate margin between worst case estimates of exposure to NVP from food, consumer goods and pharmaceutical preparations, and occupational exposures which have been shown not to be associated with serious human health effects.

The Committee concluded that the intakes of NVP from food additive uses of PVP and PVPP do not give cause for concern. The use of PVP in dietary supplements and of PVPP as a processing aid for beer and wine remain acceptable, provided the existing specifications for PVP and PVPP are amended to the currently proposed limit for NVP residues of 10 mg/kg PVP or PVPP. In order to ensure this, the Committee recommends that this specification be adopted for PVP and PVPP used in food. The Committee notes that the manufacturer supplying the European Union market currently meets such a specification.

References

BASF (1941). Unpublished report dated 29.7.1941. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1964a). Unpublished reports nos: XIII/38, XIII/139 dated 29.5.64. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1964b) Unpublished report no: XIII/38 dated 28.2.64. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1978b). Unpublished report no: 77/241 dated 30.5.78. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1986a). Unpublished project no: 42J0165/8005. Department of Toxikology, BASF AG, 6700 Ludwigshafen/rhein. Cited in HSE (2000).

BASF (1986b). Unpublished project no: 42I0186/8233 dated 12.3.86. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1986c). Unpublished project no: 12C0053/8404 dated 21.2.86. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1986d). Unpublished project no: 32C0250/8417 dated 21.2.86. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1987a). Datasheet on vinylpyrrolidone 10/87. BASF AG, 6700 Ludwigshafen/Rhein.

BASF (1987d). Unpublished project no:51I0186/8234 dated 8.12.87. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1987f). Unpublished project no: 30M0161/8616 dated 26.11.87. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1992a). Unpublished project no: 25I0242/91010 dated 29.10.92. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (1993b). Unpublished project no: 26M0133/924090 dated 26.1.93. Department of Toxikology, BASF AG, 6700 Ludwigshafen/Rhein. Cited in HSE (2000).

BASF (2000). Commission working paper SCF/CS/ADD/MsAd/184 dated 9.2.2000. Submitted by BASF AG, 6700 Ludwigshafen/Rhein.

CEFIC (2000). Communication to European Commission dated 30 May 2000.

Chandra-Gopal RM, Marti J, Mola A, Long D and Konsta A (2000). Preventing polyphenol oxidation of wine with Polyclar Ultra K-100 - a novel polyvinylpolypyrrolidone (PVPP) blend. Austr. Grapegrower & Winemaker No 438a, 102, 104-105, 107-109.

Council for Responsible Nutrition (2000). Letter to UK Food Standards Agency, dated 7.7.2000

Digenis GA (1990). Unpublished report: Disposition and pharmacokinetics of NVP, cited in HSE (2000).

Digenis GA and McClanahan JS (1982). N-vinyl-2pyrrolidinone: Disposition and metabolism studies. Toxicologist **2**: 165-166.

European Federation of Health Products Manufacturers (2000). Letter to European Commission, DG SANCO, dated 29.9.2000.

European Commission (2000). Regulation 1622/2000 Annex V/10. Official Journal L 194, 31.7.2000, p.1.

Gautier B (1995). Studies on use of PVPP with white wines. Rev.Oenol.Techn.Vitiv.Oenol. No. 78: 31.

HRC (1978c). Unpublished Ames metabolic activation test to assess the potential mutagenic effect of N-vinyl pyrrolidone. Huntingdon Research Centre, Huntingdon, Cambridge, UK. Report dated 6.4.1978, cited in HSE (2000).

HSE (2000). Risk Assessment of 1-Vinyl-2-Pyrrolidone. CAS No. 88-12-0, EINECS No. 201-800-4. Draft - May 2000. Prepared on behalf of the EU by Health and Safety Executive, Bootle, Merseyside, UK.

IARC (1999). Monographs on the evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol.71 Part III, 1181-1187. International Agency for Research on Cancer, Lyon, France.

JECFA (1983). Evaluation of certain food additives and contaminants. Twenty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series No. 696. World Health Organization, Geneva.

JECFA (1986). Specifications for identity and purity of certain food additives. FAO Food and Nutrition Paper No.37. Food and Agriculture Organization of the UN, Rome.

JECFA (1987). Evaluation of certain food additives and contaminants. Thirtieth Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series No.751. World Health Organization, Geneva.

JECFA (1988). Specifications for identity and purity of certain food additives. FAO Food and Nutrition Paper No. 38. Food and Agriculture Organization of the UN, Rome.

Klimisch HJ, Deckardt K, Gembardt C, Hildebrand B, Küttler K and Roe FJC (1997a). Long - term inhalation toxicity of N-vinylpyrrolidone-2 vapours. Studies in rats. Food and Chemical Toxicology 35: 1041-1060.

Klimisch HJ, Deckardt K, Gembardt C, Hildebrand B, Küttler K and Roe FJC (1997b). Sub-chronic inhalation and oral toxicity of N-vinylpyrrolidone-2. Studies in rodents. Food and Chemical Toxicology 35: 1061-1074.

Knaap AGAC, Voogd CE and Kramers PGN (1985). Mutagenicity of vinyl compounds. Mutation Research 147: 303.

Litton Bionetics (1980a). Unpublished LBI project no: 20989 dated Feb.1980, cited in HSE (2000).

Litton Bionetics (1980b). Unpublished LBI project no: 20991 dated April 1980, cited in HSE (2000).

Litton Bionetics (1980c). Unpublished LBI project no: 20992 dated April 1980, cited in HSE (2000).

Madigan D, Byrne H, Matthews S, Kelly R, McEnroe C and Harmey D (2000). Studies on the effects of common process variables on the colloidal stability of beer. J.Amer.Soc.Brewing Chem. 58: 180-184.

McClanahan JS, Lin YC and Digenis GA (1984). Disposition of N-vinyl-2-pyrrolidone in the Rat. Drug and Chemical Toxicology 7: 129-148.

Norpa H and Tursi F (1984). Erythrocyte-mediated metabolic activation detected by SCE. In Sister Chromatid Exchanges: 25 years of experimental research PartB Ed. Tice RR and Hollaender A. Plenum Press, New York.

SCF (1992). Reports of the Scientific Committee for Food. Twenty-sixth Series. Commission of the European Communities, EUR 13913, Luxembourg.

Simmon VF and Baden JM (1980). Mutagenic activity of vinyl compounds and derived epoxides. Mutation Research 78: 227-331.