



EUROPEAN COMMISSION
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Directorate C - Public Health and Risk Assessment
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SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS

SCHER

Opinion on

**“Risk Assessment Report on Furfural
Human Health Part”**

CAS N°: 98-01-1

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

- (1) Does the SCHER agree with the conclusions of the Risk Assessment Report?
- (2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.
- (3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

3. OPINION

The health part of the document is of acceptable quality, it is comprehensive and the exposure and effects assessment follows the TGD. The RAR covers the studies relevant for exposure and hazard assessment of furfural. Editorial aspects such as typographical errors and incomplete sentences require attention.

Human exposure to furfural may occur during occupational scenarios by inhalation and skin contact; consumer exposure may be due to skin contact or ingestion. Furfural is a natural ingredient of some fruits. The RAR uses measured data, physico-chemical properties of furfural, and information on production processes in combination with model predictions (EASE) for occupational exposure assessment. Four general scenarios for occupational exposures are evaluated for risk characterisation. Inhalation exposure is estimated based on measured data, extent of skin contact and dermal uptake is modelled. Regarding direct consumer exposure, two scenarios (skin contact from perfume and ingestion of furfural when used as flavouring substance in food) were developed. Indirect exposure via the environment is not detailed since furfural is a ubiquitous natural compound. The SCHER suggests to include an exposure estimate for furfural from natural sources.

A limited number of repeated dose toxicity studies are available and the liver is the major target organ after repeated oral administration of furfural, but liver toxicity is not very pronounced and only moderate effects have been described in a 90-day oral study in male rats. After inhalation of furfural in rats, effects on the nasal epithelium were seen even at low doses.

Negative results have been obtained in most Salmonella reverse mutation assays and other bacterial assays, but furfural is clearly genotoxic in vitro in mammalian cells, producing chromosome aberrations, gene mutations and SCEs. Genotoxic effects were not observed in in vivo assays (rat and mouse liver UDS; induction of mutations in the lacZ-gene in transgenic

animals). The negative in-vivo studies are considered valid and conclusive to support absence of genotoxicity in vivo in the target organ liver by SCHER. A briefly reported cytogenetics study claimed positive results. A study in workers which were potentially exposed to unknown concentrations of furfural did not demonstrate any significant increase in the incidence of SCEs.

Furfural caused liver tumours (carcinomas and adenomas) in male B6C3F1 mice, and increased incidences of bile duct carcinomas in male F344/N rats after oral gavage with 175 and 60 mg/kg bw/day, respectively, for 103 weeks. Significant liver lesions (chronic inflammation in mice, mild centrilobular necrosis in male rats) were observed at these exposure levels. No inhalation carcinogenicity studies in rats or mice were available. An inhalation study in hamsters (limited by its short duration of only 12 months) showed no evidence that furfural vapour had carcinogenic potential. Overall, the results indicate that furfural is carcinogenic in rodents following oral exposure. No reliable information was available on carcinogenicity in humans.

The RAR argues that the tumours are induced by a non-genotoxic mechanism since furfural did not induce genotoxicity in liver in vivo in two well performed studies and liver toxicity has been found after repeated oral furfural administration. Indeed, the development of liver tumours may be related to chronic inflammatory and cytotoxicity in the liver. However, considering the not very pronounced effects of repeated furfural administration on rat liver (described as “mild” in the 60 mg/kg dose group of male rats in the 2-year study and only “mild” effects on the liver without gross pathology in the 90-day studies applying 90 mg/kg/day by gavage and 180 mg/kg/day with diet after microencapsulation), the SCHER considers the supportive arguments for cytotoxicity as a mode of action for the liver tumours in rats as too weak and suggests a more detailed evaluation resulting in conclusion i)¹. The effects of furfural on the liver including dose-response of cytotoxicity and cell proliferation should be investigated in more detail.

Most of the MOS calculated for the worker exposure scenarios are very small and conclusion iii) is supported regarding dermal exposures and local effects; and repeated dose toxicity. Risk characterization for consumers gives MOS > 1 000. However, due to the unclear mechanisms of carcinogenicity, conclusion iii) would be warranted for consumers.

4. ACKNOWLEDGEMENTS

Prof. W. Dekant (rapporteur) is acknowledged for his valuable contribution to this opinion.

¹ According to the *Technical Guidance Document on Risk Assessment – European Communities 2003*:

- conclusion i): *There is a need for further information and/or testing;*
- conclusion ii): *There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already;*
- conclusion iii): *There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*