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

Opinion on the results of the Risk Assessment of:

HYDROGEN PEROXIDE

HUMAN HEALTH EFFECTS

CAS No.: 7722-84-1

EINECS No.: 231-765-0

REPORT VERSION: Draft of 24 April 2001

**Carried out in the framework of Council Regulation (EEC) 793/93 on
the evaluation and control of the risks of existing substances¹**

Opinion expressed at the 26th CSTEE plenary meeting

Brussels, 11 September 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.

Introduction

Hydrogen peroxide is produced in the EU by 9 companies in 22 plants (1997) and its total usage in the EU is approx. 670,000 tonnes (1995). Its main uses are in pulp bleaching (48%) and as an intermediate in the synthesis of other substances (38%), textile bleaching (7%), water treatment (3%) and miscellaneous uses (5%). Consumers may be exposed through a wide variety of products containing diluted hydrogen peroxide solutions.

GENERAL COMMENTS

The assessment follows the recommendations of the TGD and is comprehensive and properly written, though a series of typographical and formatting errors need to be corrected (e.g. text on pages 57 – 62 is included twice, typos in Ausimont, DGFG, NOAEL, Goesellschaft etc.).

The CSTEE agrees with most of the conclusions drawn. However, it does not agree with conclusion (i) regarding the request for a repeated dose inhalation animal study (for details see below, 'Risk characterisation').

Hydrogen peroxide has not been adequately tested for developmental/reproductive effects and there is no evaluation of risks to any human population for this endpoint. No adverse effects on reproductive organs have been noted in a subchronic study. Hydrogen peroxide is readily degraded and unlikely to cross the placenta and cause a direct risk to the unborn. However, if maternal respiration were severely compromised as a result of hydrogen peroxide exposure, there could possibly be an indirect effect on the foetus. Further testing, however, is unlikely to reveal any specific developmental effects.

SPECIFIC COMMENTS

Human Health

Exposure assessment

Hydrogen peroxide occurs naturally at low levels in the air and water, in human and plant tissues and bacteria, and in food and beverages. Exposure to hydrogen peroxide can occur through inhalation of the vapour or mist, ingestion, and eye or skin contact.

Hydrogen peroxide is widely used as a bleaching agent in the textile, paper and pulp industries, as an intermediate in the synthesis of other substances and in water treatment. Other uses, not mentioned in the RAR, include applications for wines and liquors (artificial ageing). The potential applications for hydrogen peroxide as a propellant are currently examined.

Exposure to hydrogen peroxide in consumer products is mainly through hair dyeing/bleaching products, household textile bleaching products, contact lens disinfectants, tooth bleaching materials, dentifrices, pharmaceutical preparations and through ingestion in food. 3% solutions are used as a sanitising mouthwash.

Hydrogen peroxide is almost always used as an aqueous solution, which is available in dilute form (3% to 10%) for household use and in concentrated form (>30%) for industrial use. Hydrogen peroxide is unstable and decomposes readily to oxygen and water. Commercial products contain a stabiliser (usually acetanilide) to slow the rate of spontaneous decomposition.

Reasonable worst case estimation for occupational exposure is between 0.14 and 2 mg/m³ 8hr TWA, with highest exposures in loading and packaging operations. A reasonable worst-case short-term exposure of 7 mg/m³ during wastewater treatment operations has been estimated. Worst-case dermal occupational exposure between 0 and 1 mg/cm²/day has been calculated with the EASE model.

Highest consumer exposures are through hair dyeing/bleaching (estimated realistic worst case: 0.24 mg/m³) and household textile bleaching (0.13 mg/m³). Ingestion through food items is estimated between 0.033 and 0.13 mg/kg bw/d. Skin/Eye contact may mostly occur through hair dyeing/bleaching, textile bleaching and tooth bleaching operations.

Human exposure indirectly via the environment is estimated as 0.28 mg/kg/d with intake from leaf crops contributing mostly to this exposure.

Effects assessment

Hydrogen peroxide is normally found in the cell and is mainly metabolised by catalase and glutathione peroxidase. Hydrogen peroxide rapidly decomposes to oxygen and water and may also produce hydroxyl radicals that can initiate lipid peroxidation and DNA damage.

Hydrogen peroxide readily passes across biological membranes, but is not well absorbed through intact skin.

The acute oral LD₅₀s for different species are in the range of 800mg/kg (90% H₂O₂) to greater than 5,000 mg/kg (10% H₂O₂). The inhalation LC₅₀ for rats is 2000 mg/m³/4h. The dermal LD₅₀s are in the range of 700 to 5000 mg/kg (90% H₂O₂). Rapid production of oxygen can occur and may cause local or systemic gas embolization.

At concentrations of 10% it is strongly irritating and concentrated solutions greater than 30% are potentially corrosive to the skin. Low concentrations (3-5%) are irritating to the eyes and

mucous membranes, while higher concentrations are severe eye irritants. Respiratory irritation was reported in volunteers exposed to 10 mg/m³ of hydrogen peroxide vapours. Skin contact with liquid hydrogen peroxide causes a temporary whitening or bleaching of the skin.

Hydrogen peroxide (3%) was not sensitising in a modified maximisation test. Two cases of positive patch testing are reported. However, given the wide occupational and consumer exposures, the potential of hydrogen peroxide to cause skin sensitisation is considered very low.

In repeated dose studies, target tissues are the sites of the initial contact.

Repeated oral exposure in drinking water caused a decrease in body weight gain in most studies and resulted in deaths of rats and mice at concentrations greater than 1%. Administration to catalase-deficient mice for 90 days produced mucosal hyperplasia in the duodenum that was completely reversible after a 6-week recovery period. No effects on reproductive organs were noted (NOAEL: 100 ppm, corresponding to 26 and 37 mg/kg/d for males and females, resp.). The NOAEL from a rat gavage study was 30 mg/kg bw.

In dogs, a species that appears to be more sensitive than the rat and mouse, repeated inhalation exposure to hydrogen peroxide vapours produced irritation, sneezing, lacrimation, bleaching of the hair and effects on the lung at doses of 10 mg/m³. Limited studies in mice and rats, exposed to 107 and 93 mg/m³, respectively, for 7 weeks and rabbits exposed to 31 mg/m³ daily for 3 months exhibited irritation, but no significant pathologic and histologic changes in the lungs and trachea.

Genotoxicity and mutations have been induced in vitro in bacteria, yeast and mammalian cells (Chinese hamster V79, mouse lymphoma cells). Chromosomal aberrations and sister chromatid exchanges were observed in human and other mammalian cells. Addition of S-9 mix or catalase abolished or markedly reduced the genotoxic responses.

In vivo micronucleus assays in mice after single intraperitoneal or 14 day oral administration were all negative, as well as an ex vivo UDS test in rat hepatocytes after intravenous infusion of hydrogen peroxide, a Drosophila sex-linked recessive lethal test and two host mediated assays in mice. IARC (1999) further reports that hydrogen peroxide did not induce chromosomal aberrations in the bone-marrow cells of exposed rats.

Hydrogen peroxide was tested for carcinogenicity in mice by oral, dermal and subcutaneous administration, in rats by oral administration and in hamsters by topical application to oral mucosa. In catalase-deficient mice, adenomas and carcinomas of the duodenum were found following oral administration in the drinking water at a dose level of approx. 300 mg/kg bw/d. In rats, no increase in the incidence of tumours was observed. The other studies in rats, mice and the study in hamsters are inadequate for evaluation. One study in mice and one study in hamsters showed no promoting activity of hydrogen peroxide.

Data on the teratogenic potential and reproductive toxicity are limited and do not allow for a complete evaluation. In mice, a dose of 1% in drinking water for 21 days, had no effect on male fertility. Rats exposed to 0.005-50mg/kg hydrogen peroxide by gavage for 6 months showed decreased sperm motility at the high dose. Only 3 out of 9 high-dose females produced litters of pups and there was a decrease in the body weights of pups. In a further,

inadequate study with Wistar rats, foetotoxicity and skeletal hypoplasia, but no teratogenicity was observed at a maternal toxic dose (10% in feed).

Risk characterisation

Workers are exposed to hydrogen peroxide by inhalation of vapour or aerosols, by skin contact or accidental splashes to the eyes. Consumers may be exposed via the gastro-intestinal tract, by skin and eye contact, and, in specific scenarios, exposure of gingiva and tooth pulp may occur.

The main concerns are for local irritant/corrosive effects and, in workers, for repeated inhalation exposure. The risk of repeated inhalation toxicity however, was not assessed in the RAR. This assessment should be performed on the basis of the available physico-chemical data, animal studies and information from health surveillance studies.

At the site of contact, hydrogen peroxide induced local irritation and duodenal tumours. Possibly, chronic inflammation is a key influence in the development of these tumours but the mechanisms involved (e.g. cell turnover, DNA repair) remain unproven. Given the low oral exposure, these findings are not considered to be of practical relevance (conclusion ii).

The CSTEE agrees with conclusion (ii) for acute toxicity, sensitisation, repeated oral/dermal toxicity, mutagenicity and carcinogenicity for all worker and consumer scenarios and indirect exposure via the environment. The conclusion also applies for irritancy/corrosivity in worker and consumer scenarios not listed below under conclusion (iii).

The CSTEE agrees with conclusion (iii) for irritancy/corrosivity in:

- Workers in loading operations and batch bleaching of textiles, aseptic packaging (old type process), peracetic acid use (brewery), etching of circuit boards (old process), metal plating, degrading of proteins and in hairdressers' work.
- Consumers in hair dyeing/bleaching and textile bleaching, if the actual concentration of hydrogen peroxide is equal or greater than 5 %.
- Risk of tooth injury if tooth bleaching is performed using concentrated (ca 35%) hydrogen peroxide (c.f. also opinion of the SCCNFP, 2000)

The CSTEE, however, does not agree with conclusion (i) for repeated inhalation toxicity testing in animals. The main reasons why a further animal study is not considered necessary, include:

- Available animal and human surveillance data. Though most of the studies are limited, they provide sufficient information for a first tier risk assessment to evaluate the risk from repeated inhalation exposure. Further retrospective (and prospective) human surveillance data/studies in occupationally exposed individuals should be used for further risk evaluation.
- Given the physico-chemical and toxicological properties of hydrogen peroxide, together with the complex detoxification/toxification mechanisms involved, and the lack of knowledge regarding toxicokinetics, the relevance of a standard animal test for the evaluation of human lung toxicity is questionable.

References

IARC, 1999. Vol. 71 Pt.2, p. 671-689

SCCNFP, 2000. Opinion on H₂O₂ in tooth bleaching agents.