UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

JUN - 7 2006

MEMORANDUM

SUBJECT: Hydrogen Peroxide –Interim Inhalation Toxicological Endpoints for Risk Assessment for uses as a fumigant in sealed room enclosures and vehicles.

EPA Reg. No.: 58779-4
PC Code: 000595
DP Barcode: D324625

FROM: Jenny J. Tao 6/5/06
Senior Toxicologist
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

TO: Marshall Swindell/Dennis Edwards
Regulatory Management Branch I/PM Team 33
Antimicrobials Division (7510P)

THROUGH: Jonathan Chen, Ph. D. Jonathan Chen 06/05/06
Senior Toxicologist
Risk Assessment and Science Support Branch
Antimicrobials Division (7510P)

and

Norm Cook, Chief 6/7/06
Risk Assessment and Science Support Branch
Antimicrobials Division (7510P)

I. ACTION REQUESTED

To assess inhalation toxicity of hydrogen peroxide for the proposed use in sealed room enclosures and vehicles.

II. BACKGROUND

The registrant (STERIS® Corporation) has submitted a petition for the use of the product *Vaprox*® Hydrogen Peroxide Sterilent containing 35% hydrogen peroxide in sealed room enclosures and vehicles. The registrant proposes to amend the current label with the following statement:

> "This product is intended for use as a non-medical/non-healthcare sterilant (i.e., for industrial use only). This product is for use in STERIS VHP® industrial equipment only, and by trained personnel. For sterilization of empty, pre-cleaned, sealed enclosures up to 40 ft^3, apply 2.2 grams of product per minute for 90 minutes."

The proposed use is indoor non-food use only, which is no different to the currently approved uses, with only exception of a larger treatment area.

The registrant did not submit any mammalian toxicity data. The registrant states that in the proposed applications, the treatment areas will be closed systems, and even though the VHP application equipment for the proposed uses may be placed in the sealed enclosure, it will be operated remotely or operated from outside the sealed enclosure. Inhalation is identified as the primary potential route of exposure.

This memorandum RASSB will assess the toxicological concern associated with exposure to hydrogen peroxide through inhalation route. In addition, appropriate inhalation toxicological interim endpoints will be selected for risk assessment for using hydrogen peroxide as a fumigant in sealed room enclosures and vehicles.

III. RESULTS/DISCUSSION

A. Inhalation Toxicological Concerns of Hydrogen Peroxide

Hydrogen peroxide is a strong oxidant. The data from a wide variety of experiments have suggested that reactive oxygen metabolites may play an important role in the pathophysiology of lung inflammation and injury, and evidence has shown formation of short-lived reactive oxygen species within the lung tissue in many types of lung injury.

Misawa and Arai (1993) noted inhalation of hydrogen peroxide (0.01, 0.1 and 1.0 M) markedly caused a pontamine sky blue (PSB) exudation in a concentration-dependent manner in the trachea, main bronchus, and lungs. The airway vascular permeability in response to hydrogen peroxide was observed immediately after the end of inhalation of hydrogen peroxide, and the hydrogen peroxide-induced PSB exudation was significantly attenuated by pretreatment with catalase in a concentration-dependent manner (300, 3000 U/ml). These results indicate that hydrogen peroxide causes an intensive airway inflammation.

There is a 28-day inhalation study in rats conducted by the industry (CEFIC Peroxygen Sector Group, 2002, cited in European Union (EU) risk assessment report of H_2O_2). Although it is cited as a range finding study for a 90-day inhalation study, RASSB considers it is an appropriate study for interim end-point selection for inhalation exposure.

B. Interim Inhalation End-point Selection for Hydrogen Peroxide

When hydrogen peroxide is applied as a fumigant, inhalation may be the primary potential exposure route. Since the registrant did not submit any inhalation study, RASSB selected interim end-points based on studies cited in literature for this risk assessment.

B.1 Short–Term (0 – 30 days) Inhalation Exposure and Intermediate–Term Inhalation (30 Days to Six Months) Exposure

Study Selected: 28-day rats inhalation study (CEFIC Peroxygen Sector Group, 2002, cited in EU risk assessment report of H_2O_2

Executive Summary: Groups of five male and female Alpk:AP$_f$SD (Wistar-derived) rats were exposed whole-body for 6 hours per day to 0 (control), 2.9, 14.6 or 33 mg/m^3 hydrogen peroxide vapor for 5 days per week, for a period of 28 days. Clinical signs that demonstrated respiratory tract irritation were seen at the exposure levels of 14.6 and 33 mg/m^3, but not at 2.9 mg/m^3. Regarding histopathology (see **Table 1**), necrosis and inflammation of the epithelium in the anterior regions of the nasal cavity were found at the two higher concentration levels. In the larynx, mononuclear cell infiltration was seen in two females at the highest exposure concentration. Moreover, one male rat in each exposure group and two female rats in the high concentration group exhibited perivascular neutrophil infiltration in the lungs, and hemorrhage was found in some animals at the two lower concentration levels. RASSB believes 2.9 mg/m^3 would be the LOAEL for the study based on the pathological findings in the respiratory tracts (inflammation in the larynx and increased incidences of hemorrhage and perivascular neutrophil infiltration in the lungs).

Dose and Endpoint for Risk Assessment: Inhalation toxicity **LOAEL** of 2.9 mg/m^3 based on pathological findings in the respiratory tracts (inflammation in the larynx and increased incidences of hemorrhage and perivascular neutrophil infiltration in the lungs).

Comments about Study/Endpoint: The EU believed the nasal localization of the primary injury by peroxide is what can be expected from a water soluble oxidant vapor. As regards pathology in the lungs, the authors of the study considered it unlikely that the effects were treatment related due to the absence of a relationship with exposure concentration and the low incidence, and hence EU identify the 2.9 mg/m^3 as the **NOAEL** of the study. Since the study report is not available to the Agency, RASSB can not assess the severity of the pathological effects identified in the study. However, the findings were consistent and persistent throughout all treatment groups. RASSB believes 2.9 mg/m^3 should be identified as **LOAEL** of the study given the fact that hydrogen peroxide and/or its immediate degradation products (reactive oxygen species) are strong oxidants and can cause airway inflammation (Misawa and Arai, 1993).

Table 1. Summarized microscopic findings of the respiratory system in the 28-day inhalation study in rats (CEFIC Peroxygen Sector Group, 2002)

Target Organ	Microscopic Findings			
	0 mg/m^3	2.9 mg/m^3	14.6 mg/m^3	33 mg/m^3
Nasal cavity	–	–	Necrosis* and inflammation (squamous epithelium, anterior regions of nasal cavity) 3/5 M, 2/5F	Rhinitis 1/5 M Necrosis* and inflammation (squamous epithelium, anterior regions of nasal cavity) 4/5M, 4/5F
Larynx	–	Inflammation 1/5F		Mononuclear cell infiltration 2/5F Epithelial erosion 1/5M
Lung	–	↑Perivascular neutrophil infiltration 1/5M Hemorrhage 2/5M, 1/5F	↑Perivascular neutrophil infiltration 1/5M Hemorrhage 2/5M	↑Perivascular neutrophil infiltration 1/5M, 2/5F

- indicates no findings

* Necrosis in the context of this report means the more common type of cell death following external stimuli (cf. apoptosis), manifested by severe cell swelling or rupture, denaturation & coagulation of cytoplasmic proteins and breakdown of cell organelles

F - female; M – male

B.2 Long–Term Inhalation (> Six Months) Exposure

No appropriate interim end-point selected for long–term inhalation exposure.

C. Margin of Exposure (MOE) for Occupational/Residential Risk Assessments

A MOE of 300 is selected for short-term and intermediate-term inhalation assessment. (3x for LOAEL to NOAEL, 10x for intra-species, and 10x for inter species).

IV. SUMMARY

Table 2 summarizes the interim inhalation toxicological endpoints and target margin of exposure (MOE) selected for risk assessment for using hydrogen peroxide as a fumigant in sealed room enclosures and vehicles.

Table 2. Interim Inhalation Toxicology Endpoints for Risk Assessment for Hydrogen Peroxide

Exposure Scenario	Dose Used in Risk Assessment and Toxicological Effects	Target MOE	Study
Short-term [0 to 30 Days] and Intermediate-term [30 Days to 6 Months]	LOAEL = 3.0 mg/m^3 based on pathological findings in the respiratory tracts (inflammation in the larynx and increased incidences of hemorrhage and perivascular neutrophil infiltration in the lungs)	MOE = 300 (occupational and residential) (3x for LOAEL to NOAEL, 10x for intra-species, and 10x for inter species).	28-day rats inhalation study (CEFIC Peroxygen Sector Group, 2002, cited in EU risk assessment report of H_2O_2)
Long-term [> 6 month]	Not selected		

V. REFERENCES

CEFIC 2002. Hydrogen Peroxide: 28-day Inhalation Study in Rats. CTL/MR0211/Technical Toxicology/Report. Central Toxicology Laboratory, Alderley Park Macclesfield. CEFIC Peroxygen Sector Group (cited in EU Risk Assessment Report: hydrogen peroxide. 2003).

EU Risk Assessment Report: hydrogen peroxide. 2003. European Chemicals Bureau – Existing Chemicals, Vol. 38.
http://ecb.jrc.it/DOCUMENTS/ExistingChemicals/RISK_ASSESSMENT/REPORT/hydrogenperoxidereport022.pdf

Misawa , M and Arai H. 1993. Airway inflammatory effect of hydrogen peroxide in guinea pigs. J. Tox. Environ. Health, 38:435-448.