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Target Audience:  
 AFQ Inspectors  
 SG Medical Inspectors, Occ Health, Occ Hygiene

## **ENDOSCOPE DISINFECTION - ALTERNATIVES TO GLUTARALDEHYDE**

This SIM describes recent reviews of the health affects of succinic dialdehyde, ortho-phthalaldehyde and peracetic acid, which were discussed at the WATCH sub-group meeting of the Advisory Committee on Toxic Substances. WATCH decisions on the potential ill-health affects should be considered when assessing employers' choice of cold sterilization chemicals, in particular under the Control of Substances Hazardous to Health.

1 There is a range of instruments, particularly flexible endoscopes, that cannot be sterilized by 'traditional' means of autoclaving, due to sensitive nature of the imaging equipment within them. There are a number of products on the market which are used to sterilize such equipment, including such substances as glutaraldehyde, peracetic acid, chlorine dioxide, superoxidated water, as well as o-phthalaldehyde bases such as succinic dialdehyde (SDA) and o-phthalaldehyde (OPA).

2 A maximum exposure level was set for glutaraldehyde in March 1999. The MEL has a value of 0.05 ppm 8-hour TWA and 0.05 ppm 15-minute reference period. Glutaraldehyde is an acute sensitizer, therefore no 'safe level' can be set. The control of exposure can only be regarded as adequate if exposure levels are reduced so far as is reasonably practicable, and for inhalation in any case below the MEL.

3 Following the withdrawal of CIDEX (a proprietary preparation containing glutaraldehyde manufactured by Johnson & Johnson) in May 2002, the Health Services Unit (HSU) requested that the Industrial Toxicological Unit (ITU) consider the toxicological properties of some of the new alternative cold sterilizing substances coming onto the market.

4 Industrial Toxicological Unit considered peracetic acid, succinic dialdehyde (SDA) and o-phthalaldehyde (OPA). Papers were tabled at the October meeting of the WATCH sub-group meeting of the Advisory Committee on Toxic Substances, [see Appendix 1](#) (NB: these are long documents).

5 The research identified from the limited information available and a consideration of

the chemical structures, that ortho-phthalaldehyde and succinic dialdehyde may have the potential to cause occupational asthma. WATCH made the following statement regarding the health risks of these substances:

"WATCH noted that there was very little information on the toxicological properties of succinic dialdehyde and ortho-phthalaldehyde. On the basis of the information that is available, WATCH concluded that both substances may have the potential to cause occupational asthma, It recommended that control strategies for both substances should take account of this potential health hazard."

6 It should be noted that these conclusions apply to the active ingredients OPA and SDA only. There was no assessment of the likely health problems arising from the formulated commercial products containing these ingredients. Further information on the potential for these substances to become airborne and lead to inhalation exposure is needed before a judgement on the likely occupational health risks can be made.

7 Central approaches are being made to the manufacturers of products containing these substances to encourage further research into their toxicological properties.

8 Papers authored by ITU on peracetic acid were also tabled at the October meeting of WATCH, [Appendix 2](#). (NB these are long documents).

9 Research identified peracetic acid is highly corrosive, and WATCH concluded that the key occupational health concern was local site-of-contact irritation. The evidence suggested that even very low airborne concentrations would be able to cause eye and throat irritation, but the data did not allow any reliable quantification of these concentrations. WATCH made the following statement regarding the health affects of peracetic acid:

"WATCH concluded that the key concern from peracetic acid was local site-of-contact irritation. In addition to the potential of peracetic acid to provoke upper respiratory tract sensory irritation, WATCH considered that it may also have the potential to produce chronic lung inflammation, but there was no data to confirm or refute this supposition. WATCH considered that the available data did not enable a threshold for these effects to be identified with any accuracy or confidence. However, such a threshold would certainly lie below the irritant threshold for hydrogen peroxide."

10 Inspectors will wish to ensure that organisations are made aware of these recent developments, and that such information is considered as part of a suitable and sufficient assessment of the potential for substitution of existing cold sterilization chemicals.

Date first issued: 9 April 2003

**TOP A**

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APPENDIX 1  
(para 4)

WATCH PAPER ON SUCCINIC DIALDEHYDE & O-PHTHALALDEHYDE

Paper Number: WATCH/20/2002  
Meeting Date: 19 September 2002

**HEALTH AND SAFETY COMMISSION**  
**ADVISORY COMMITTEE ON TOXIC SUBSTANCES**  
**WATCH SUB-COMMITTEE**  
**CHEMICAL SUBSTITUTES FOR GLUTARALDEHYDE IN**  
**STERILISATION OF MEDICAL EQUIPMENT**

**Issue**

1. Toxicological hazard assessment of two potential alternatives to glutaraldehyde in the sterilisation of medical equipment.

**Timing**

2. A position from WATCH is required at the September 2002 meeting.

**Recommendation**

3. WATCH is invited to respond to the actions in [paragraph 15](#).

**Background**

4. Glutaraldehyde was examined by WATCH in the mid-1990s. As a consequence, glutaraldehyde has MELs of 0.05 ppm (8-hour TWA and STEL) and is also assigned a Sen notation in recognition of its classification as a respiratory sensitiser in the EU. The MELs for glutaraldehyde were first implemented in EH40 in 1999. According to the ODIN scheme (SWORD and OPRA) there were 40 cases **per year** of occupational asthma attributed to glutaraldehyde reported by participating chest and occupational physicians in the period 1999-2001. This accounts for 4.6% of all new cases, the fifth highest percentage for a specified agent (isocyanates, flour/grain, latex and wood dust being the top 4). The vast majority of glutaraldehyde cases were nurses and other health care workers. In May this year, the main glutaraldehyde-containing product (CIDEX<sup>®</sup>), an aqueous solution containing 2.4% glutaraldehyde, was withdrawn from the market. In view of this, hospitals and veterinary practices will be looking to use alternative sterilant systems.

5. As with other substitution decisions, there is an issue about the extent of knowledge of the toxicological properties of the potential alternatives. Some of the principal alternative active ingredients to glutaraldehyde do not have established UK or EU regulatory positions with respect to hazard classification or occupational risk management (OELs etc). Given the concerns about asthma with glutaraldehyde, a key issue is the asthmagenic potential of

such alternatives, particularly as occupational asthma is a priority area for HSE's work on chemicals.

6. In view of this situation, HSE's Field Operations Division (FOD) recently requested advice on the likely occupational health hazards of the main chemical sterilants available as alternatives to glutaraldehyde. It is intended that FOD's Health Services Unit will provide this advice to the Health Services Advisory Committee (HSAC) as a contribution to a broader debate on sterilant systems for use in health care. The HSAC discussion will also need to take account of factors such as efficacy and costs, as well as ease of use, health hazards and appropriate control strategies. This WATCH project is not intended to cover all such issues, but is focused on providing an essential foundation stone in developing a view on the health hazards of the alternative active ingredients. The work will also make an important contribution to the asthma strategy. The asthma plan of actions outlines a programme of work to reduce the incidence of occupational asthma due to glutaraldehyde to zero by 2005, by substitution with suitable alternatives.

7. In developing this project, staff in HSE's Industrial Chemicals Unit took advice from HSE inspectors in the health services sector and searched information sources in this medical field to identify the main chemical alternatives to glutaraldehyde. Manufacturers and suppliers were contacted in an attempt to obtain all possible toxicological data on the active ingredients and their formulations; independent literature searches were also undertaken. The main alternative active ingredients identified were succinic dialdehyde (SDA), ortho-phthalaldehyde (OPA), and peracetic acid. Different commercial formulations based on these active ingredients, and also a very dilute hypochlorous acid-based formulation (Sterilox<sup>®</sup>), are marketed for sterilising endoscopy equipment. As there are no problematic issues concerning the toxicology assessment for the Sterilox<sup>®</sup> product it has not been included in this WATCH package. A number of enzyme-based sterilant products were also identified but it is not known yet whether they have gained any use in UK hospitals, and these products have also not been included in this project.

8. The technical package accompanying this Cover Paper covers the toxicology of SDA and OPA. A separate HSE package on peracetic acid (WATCH/19/2002) is also available for discussion at this September 2002 WATCH meeting.

9. There are no UK OELs listed for SDA or OPA and HSE does not propose to develop OELs for them at this stage. Furthermore, neither SDA nor OPA are listed in the Approved Supply List with an agreed EU classification. In such situations, it is the suppliers'/manufacturers' responsibility to self-classify. At this stage, HSE does not intend to develop a formal classification proposal for SDA or OPA. Rather, the intention is to develop a view on the known and (where data are lacking) potential occupational health hazards of these substances; in particular, to give a view on whether they might be capable of causing occupational asthma.

10. The documentation provided with this cover paper is as follows:

**Annex 1:** HSE Health hazard assessments of SDA ([Section 1](#)) and OPA ([Section 2](#)).

*Argument*

Health hazards

11. Very few toxicological studies have been conducted on SDA and OPA. In relation to

occupational asthma, SDA is a dialdehyde that is structurally very similar to glutaraldehyde, being only one carbon atom less in chain length. There are no data concerning the ability of SDA to cause asthma. On structure-activity grounds one might predict that it might have the potential to cause asthma in a manner similar to that of glutaraldehyde. Currently, there are no documented case-reports of occupational asthma in workers exposed to SDA. However, it is uncertain how long SDA-containing formulations have been used for endoscopy sterilisation or how widespread the use of these formulations has become. SDA is present as an active ingredient in two commercial formulations used in the UK (Gigasept<sup>®</sup> containing 6.8% SDA, and Gigasept<sup>®</sup> FF containing 11% SDA).

12. OPA is also a dialdehyde; it is the active ingredient in the commercial formulation Cidex-opa<sup>®</sup> (containing 0.56% OPA). As with SDA, there are no data concerning the ability of OPA to cause asthma. The chemical structure of OPA consists of two aldehyde groups adjacent to each other on a benzene ring. The influence that the benzene ring might have on the ability of OPA to cross-link with proteins to form an immunologically active conjugate is uncertain. However, Cidex-opa<sup>®</sup> appears to be a relatively fast-acting sterilant, effective even at such a low concentration of the active ingredient (OPA). This suggests a high degree of chemical reactivity for OPA as a cross-linking agent to proteins. In support of this, marketing information indicates that Cidex-opa<sup>®</sup> kills most microorganisms within 5-12 minutes of contact. This observation, together with the fact that another dialdehyde (glutaraldehyde) is a known asthmagen, might raise some concern about its potential to cause asthma.

### **Consultation**

13. No consultation beyond HSE has been undertaken at this stage. HSE have informed the Department of Health and the Scottish and Welsh offices that this review is being undertaken.

### **European Implications**

14. There are no European implications for this work.

### **Action**

15. WATCH is asked to consider the attached documentation and:

- i. Give a view on the known and, in the absence of data, what might be positively indicated as possible health hazards of the active ingredients SDA and OPA.

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## **Health Hazard Assessments for.**

**Succinic Dialdehyde**

**and**

**ortho-phthalaldehyde**

**HSE September 2002**

## Health Hazards Assessments for succinic dialdehyde and ortho-phthalaldehyde

### Background

WATCH discussed the health hazards of glutaraldehyde in the mid-1990s (WATCH/1/97) and concluded that it was an asthmagen and a respiratory tract irritant. As a consequence of the WATCH/ACTS discussions and in recognition of its classification as a respiratory sensitiser in the EU, MELs of 0.05 ppm (8-hour TWA and STEL) and a Sen notation were assigned to glutaraldehyde. The MEL position was implemented (i.e. first published in EH40) in 1999. However, glutaraldehyde is still a major cause of occupational asthma among health care workers; according to the ODIN scheme (SWORD and OPRA) there were 40 cases per year of occupational asthma attributed to glutaraldehyde reported by participating chest and occupational physicians in the period 1999-2001. This accounts for 4.6% of all new cases, the fifth highest percentage for a specified agent (isocyanates, flour/grain, latex and wood dust being the top 4).

In May this year, one of the main glutaraldehyde-containing products used for endoscope sterilisation, Cidex<sup>®</sup> (containing 2.4% glutaraldehyde), was withdrawn by the manufacturers from the UK market. This will inevitably lead to an increase in the use of alternative products. Some of these alternatives also contain glutaraldehyde, (for example Gigasept<sup>®</sup> Rapid), but there are a number of other products available that contain chemicals other than glutaraldehyde as their active ingredients; these chemicals include peracetic acid, succinic dialdehyde (present in certain Gigasept<sup>®</sup> formulations at up to 11%), ortho-phthalaldehyde (present at 0.56% in the commercial product Cidex-opa<sup>®</sup>).

Unlike the case with glutaraldehyde, there has been only very limited toxicological testing of these alternative substances and their formulations, and there is almost no documented information concerning human exposures. A particular issue for these alternatives to glutaraldehyde is that of their asthmagenic potential; given the HSE-led Securing Health Together initiative to reduce the incidence of occupational asthma by 30% by the year 2010, HSE believes that the asthmagenic potential of these alternative substances needs to be factored into any substitution (for glutaraldehyde) decisions.

In view of the potential for a substantial increase in the use of these alternative sterilant products, HSE's Field Operations Directorate (FOD) recently requested a review of their human health hazards. FOD would like to include this review in advice to be given to the Health Services Advisory Committee (HSAC) as a contribution to a broader discussion on sterilant systems for use in the NHS. The HSAC discussion will take account of additional factors such as efficacy and costs, as well as ease of use, health hazards and appropriate control strategies. The eventual aim will be to rank the various sterilant products according to the above factors to enable HSAC to make recommendations to the NHS on which sterilant products best meet its needs. This WATCH review, produced by HSE's Industrial Chemicals Unit, covers only the human health hazards.

Prior to the request for this review from FOD, an HSE review of peracetic acid had already begun. The peracetic acid review will be taken as a separate agenda item at this WATCH meeting (September 2002). This document provides an HSE assessment of the toxicological profiles of succinic dialdehyde (Section 1 pages 1-15), and ortho-phthalaldehyde (Section 2 pages 1-13). The views from WATCH concerning the health hazard assessment of peracetic acid will be provided to FOD, alongside the views from WATCH on succinic dialdehyde and ortho-phthalaldehyde.

## SECTION 1: Succinic Dialdehyde

### 1 Summary

#### 1.1 Toxicity of succinic dialdehyde

The toxicological database on succinic dialdehyde (SDA) is very sparse, largely deriving from a handful of unpublished industry-sponsored studies. There are no meaningful data relating to the effects of inhalation exposure, and no studies concerning the effects of repeated exposure, mutagenicity, carcinogenicity or reproductive toxicity. In view of the paucity of toxicological data for SDA, a "read-across" approach to the structurally similar compound glutaraldehyde has been explored.

There are no data on the toxicokinetics of SDA. Based on its dialdehyde structure and by analogy with glutaraldehyde, it would be predicted that SDA would bind to tissues at the site of contact, thereby limiting systemic uptake from occupationally relevant exposure routes. It would also be predicted that any absorbed SDA would be rapidly metabolised to CO<sub>2</sub> and therefore would be unlikely to bioaccumulate on repeated exposure.

There is no information on the effects of single exposures in humans and there are no reliable animal studies of its acute inhalation toxicity. Results from acute oral studies reveal that SDA is toxic by this route; LD<sub>50</sub> values in rats fall in the range 50 – 75 mg SDA/kg. A study in rats indicates that SDA is of low systemic toxicity via the dermal route of exposure, with the only effects observed consisting of local damage at the site of application. The acute oral and dermal toxicity data for SDA are qualitatively and quantitatively similar to those for glutaraldehyde. Hence, given the similarity in their chemical structures, it seems reasonable to assume that the inhalation toxicities of the substances would also be broadly similar, suggesting that SDA is likely to be toxic on single inhalation exposure. For all exposure routes, toxic effects are likely to be largely a consequence of severe irritancy/inflammation at the site of contact.

There is no information on the irritancy of SDA in humans. Studies in animals indicate that SDA is a severe eye irritant and a strong skin irritant. Given the effects seen in these studies and by analogy with glutaraldehyde, it is likely that SDA would also cause sensory irritation and inflammation of the respiratory tract. From the information available it is not possible to predict what the threshold airborne concentration of SDA would be for the elicitation of sensory irritation in humans.

The sensitising properties of SDA have not been adequately investigated. Its chemical structure and similarity with glutaraldehyde suggest that SDA may have both skin sensitising and asthmagenic potential.

No studies have been conducted in either humans or experimental animals to determine the effects of repeated exposure to SDA. For glutaraldehyde, studies in rats and mice indicate that the upper respiratory tract is the key target site of toxicity following repeated inhalation exposure. A NOAEL has not been identified for glutaraldehyde, with evidence of nasal epithelial inflammation at the lowest concentration tested (0.0625 ppm). Based on the similar chemical structures and similar irritant properties that have been identified for SDA, it is probable that upper respiratory tract irritation will also be a key feature for this substance. However, it is not possible to predict in quantitative terms what the likely dose-response relationships would be for SDA.

No mutagenicity studies have been reported for SDA. Information on glutaraldehyde

reveals that it is a direct-acting mutagen in bacterial and mammalian cells *in vitro*, suggesting that SDA will also possess this property. The evidence from studies *in vivo* is somewhat patchy. Negative results have been obtained for glutaraldehyde in good-quality bone marrow cytogenetics, peripheral blood micronucleus and liver UDS assays *in vivo*, providing reassurance that the genotoxic effects of glutaraldehyde *in vitro* are unlikely to be expressed *in vivo* at tissues distal to the site of contact. However, the potential for genotoxicity at the site of contact has not been examined. It is not clear from these findings whether or not SDA would have the potential to induce mutagenic effects *in vivo*. However, the overall pattern of results for this series of dialdehydes is not reassuring.

There are no studies into the carcinogenic potential of SDA. For glutaraldehyde there was no evidence of carcinogenicity in a recent two-year inhalation study in rats and mice; evidence of irritant damage of the nasal epithelia was present at all concentrations tested in both species, providing reassurance of a lack of carcinogenic potential when tested at cytotoxic concentrations. In the absence of data for SDA, it seems reasonable to predict that the carcinogenic profile of these two substances would be broadly similar.

In relation to reproductive toxicity, no studies have been conducted with SDA. However, given that the systemic absorption of SDA is likely to be very limited due to binding with tissues at the site of contact, it is unlikely that there would be any significant exposure of the reproductive organs following occupational exposure to this substance. Hence, there are no grounds to consider that SDA would be a reproductive toxicant. In support of this, there was no evidence from fertility and developmental toxicity studies with glutaraldehyde for effects on these endpoints.

## Succinic Dialdehyde

### 2 Introduction

Succinic dialdehyde (SDA) has a chemical structure very similar to glutaraldehyde, being only one carbon atom less in chain length. A very thorough search has been undertaken by HSE to identify toxicity data on SDA, including a full literature search of all the main medical and toxicological databases, and contacting the UK suppliers of SDA itself. Relatively few studies were traced. In view of the paucity of toxicological data for SDA, the potential for a "read-across" approach to the data on the structurally similar compound glutaraldehyde (HSE, 1997) has been explored throughout this document. No Occupational Exposure Limits have been set for SDA in the UK and none have been identified in other countries. There is no EU-agreed classification for SDA listed in the Approved Supply List.

The structural formulae of succinic dialdehyde and glutaraldehyde are given as follows:

**Succinic dialdehyde:** CHO.CH<sub>2</sub>.CH<sub>2</sub>.CHO

**Glutaraldehyde:** CHO.CH<sub>2</sub>.CH<sub>2</sub>.CH<sub>2</sub>.CHO

**Table 1. Physicochemical properties of succinic dialdehyde and glutaraldehyde**

	Succinic dialdehyde	Glutaraldehyde
Molecular Formula	C <sub>4</sub> H <sub>6</sub> O <sub>2</sub>	C <sub>5</sub> H <sub>8</sub> O <sub>2</sub>
Molecular Weight	86	100
Physical State	Liquid	Liquid/Oil
Melting point	-16°C*	-14°C

		(Freezing point)
Boiling point	98°C*	187 - 189°C
Vapour pressure	0.22Kpa at 20°C*	0.002 Kpa at 20°C (50% solution)

\* Taken from supplier's material safety data sheet – the authenticity of these values has not been validated by HSE.

### 3 Identification

Chemical Name:	Succinic dialdehyde
Synonyms:	Succinic aldehyde Succindialdehy Succinaldehyde Succine aldehyde Succine dialdehyde 1,4-Butanedial 1,4-Butanedione
CAS No.:	638-37-92
EINECS No.:	11-333-8
Molecular Formula:	C <sub>4</sub> H <sub>6</sub> O <sub>2</sub>
Molecular Weight:	86.09
Physical state:	Liquid, light yellow in colour
Melting point:	-16 °C
Boiling point:	98 °C
Density:	1.109 g/cm <sup>3</sup>
Vapour pressure:	0.22 Kpa at 20°C
Solubility:	Fully miscible with water
Conversion factor:	1 ppm = 3.6 mg.m <sup>3</sup> at 25°C

**Table 2. Composition of commercial formulations containing succinic dialdehyde**

Gigasept <sup>®</sup>	Gigasept <sup>®</sup> FF
6.8% succinic dialdehyde	11% succinic dialdehyde
4.5% dimethoxytetrahydrofuran	3 % dimethoxytetrahydrofuran
4.5% formaldehyde	10-30% ethanol
3-8% methanol	10-20% propan-1-ol
25-45% ethanol	5-10% methanol

### 4 Toxicokinetics and Toxicology

#### Toxicokinetics

Dialdehydes contain two aldehyde (-CHO) functional groups. These aldehyde groups confer cross-linking properties on the molecule, demonstrated by the fact that aldehydes are very effective fixatives for proteins and nucleic acids (ITG, 2001). The established cross-linking properties of aldehydes and dialdehydes suggests that SDA would have the propensity to covalently bind to biological molecules in tissues at the site of contact.

No studies have been conducted to investigate the toxicokinetic profile of SDA in either humans or animals. There is also relatively little information on the toxicokinetics of glutaraldehyde, with no data concerning the extent of absorption via inhalation or oral exposure. Based on its dialdehyde structure and by analogy with glutaraldehyde, it would be predicted that following inhalation exposure SDA would bind to tissues at the site of contact. Similarly, absorption across the skin is likely to be limited due to binding at the site of contact (as observed for glutaraldehyde). It is uncertain whether there would be any significant systemic uptake of SDA following oral ingestion. Some passage into the systemic circulation via damaged skin or damaged gastro-intestinal epithelium might be possible. Overall, little or no systemic uptake of SDA would be expected to occur from occupationally relevant exposure routes. Experimental data on glutaraldehyde shows that following parenteral administration, it is rapidly metabolised to CO<sub>2</sub>. It is likely that any SDA absorbed into the systemic circulation would be similarly rapidly metabolised. These considerations suggest it is unlikely that there will be any significant exposure of the reproductive organs and developing foetus following occupational exposure to SDA. Also there are no grounds to consider that SDA would bioaccumulate on repeated exposure or that it would be eliminated in breast milk.

## 4.2 Acute Toxicity

### 4.2.1 Studies in animals

#### Inhalation

One unpublished inhalation study was available, of which very scant details were reported (Kodak, 1958/68a). The only information in this report was given as follows: "Three rats exposed to 15 mg/L (15 ppm, nominal concentration) for 6 hours exhibited no clinical signs. Three rats exposed to 76 mg/L (76 ppm) of the aqueous solution for 6 hours showed slight nasal discharge, but no other clinical signs. The test was repeated at 50°C, 106 mg/L for 6 hours and again, no clinical signs were observed. An inhalation LC<sub>50</sub> was not established."

It was not stated whether any pathological examinations were conducted, or for how long post-exposure the animals were observed. Current protocols require a 14-day post-exposure observation period. The accuracy of the cited exposure concentrations is unknown, particularly as no mention was made of any analysis to confirm the nominal concentrations, and there were no details of how the exposure atmospheres were generated which might have shed some light on the reliability of the reported nominal concentrations. Also, it is unknown as to whether or not the exposures were to aerosols of SDA (and if so whether the aerosol droplets were in the inhalable size range), or to vapour, or to a mixture of both. Overall, it is not possible to draw any meaningful conclusions about the acute inhalation toxicity of SDA from this old and brief report.

However, given the qualitative and quantitative similarities in the acute oral toxicity data for SDA and glutaraldehyde, it might be expected that their acute inhalation toxicities would also be broadly similar. For glutaraldehyde in rats, 4-hour LC<sub>50</sub> values for the aerosol of 0.28 – 0.8 mg.l<sup>-1</sup> were reported, and 6 – 8-hour LC<sub>50</sub> values for the vapour fall within the 0.092 - 0.160 mg.l<sup>-1</sup> range. Decedents showed signs of severe pulmonary damage. No macroscopic lesions were visible in animals that survived the 14-day post exposure observation period.

#### Oral

Oral LD<sub>50</sub> values for SDA have been determined for solutions of varying strengths. In an oral LD<sub>50</sub> study conducted to OECD guidelines, groups of Wistar rats (5/sex) were given doses of a 40% solution (presumably aqueous) of SDA and observed for 14 days (IBR Forschungs GmbH, 1989a). Only a summary report for this study is available. The numbers of deaths and dose levels at which animals died were not stated. Animals that died during the 14-day observation period showed signs of fluid retention and irritation of the gastrointestinal tract. No abnormalities were apparent in surviving animals at study termination. An LD<sub>50</sub> value of 171 mg/kg was calculated for the 40% solution (equivalent to around 68 mg SDA/kg). These results suggest that the main effect of single oral exposure to SDA is local damage to the gastrointestinal tract. Oral LD<sub>50</sub> values in the rat for glutaraldehyde when given as a 50% aqueous solution range from 140 – 700 mg glutaraldehyde/kg, the main effect also being gastrointestinal tract irritation (Ohno *et al*, 1991, Ballantyne *et al*, 1986, BASF, 1981). This suggests that the acute effects of SDA are at least as severe as those of glutaraldehyde on oral dosing.

In another unpublished study conducted between 1958 and 1968, the single oral dose toxicity of more dilute solutions of SDA was assessed in rats and mice (Kodak, 1958/68b). Few details were reported. LD<sub>50</sub> values in rats for SDA given as 12 and 25% solutions (presumably aqueous) fell within the range 50 – 75 mg/kg. It was not specified whether these values were for the solution or were expressed as the SDA content of the solution. However, HSE surmises that the values were most likely for the SDA content. In mice, LD<sub>50</sub> values for SDA given as 25 and 1% solutions (presumably aqueous) fell within the range 100 – 200 mg/kg. Again, it is assumed that these values relate to SDA itself and not to the total preparation. It is not clear if any pathological examinations were performed. For comparison, LD<sub>50</sub> values for 10 – 25% aqueous solutions of glutaraldehyde range from 111 – 633 mg glutaraldehyde/kg. It is noted that the more dilute solutions have lower LD<sub>50</sub> values (i.e. were more toxic); this was particularly noticeable in one study in which LD<sub>50</sub> values for a range of glutaraldehyde solutions of varying strengths had been determined (Ballantyne, 1986). In mice, LD<sub>50</sub> values for 1, 2 and 25% aqueous solutions range from 30 – 350 mg glutaraldehyde/kg. Again, the more dilute solutions yielded lower LD<sub>50</sub> values. The reason for the apparently increased toxicity of the more dilute solutions of glutaraldehyde appears to be that dimerisation of glutaraldehyde molecules occurs to a greater extent with more concentrated solutions, thereby reducing its availability.

Overall, it appears as though there is a broad overlap in the acute oral toxicities of these dialdehydes.

## Dermal

In a dermal LD<sub>50</sub> test conducted to OECD guidelines, 2000 mg/kg of a 40% solution (presumably aqueous) of SDA (equivalent to 800 mg SDA/kg) was applied to the skin of 5 male and 5 female Wistar rats for 24 hours and animals were observed for 14 days (IBR Forschungs GmbH, 1989b). Only a summary report for this study is available. No deaths occurred. Erythema, oedema and punctate scabbing were clearly present at the site of application (scores were not reported). No other outward signs of toxicity were apparent. Animals gained weight normally during the observation period and there were no findings at necropsy. This study suggests that the main effect of dermal exposure to SDA is skin damage at the site of contact.

In another unpublished study conducted between 1958 and 1968, the effects of single

dermal exposure to SDA were assessed in three animals (species unspecified) (Kodak, 1958/68c). Aqueous solutions, with concentrations ranging from 1 – 25% were used (duration of exposure and nature of dressing at the site of application not reported). The wording of the report implies that the different concentrations were applied to the three animals simultaneously, although this is not explicitly stated. Irritation was observed at all concentrations and the severity increased with increasing dose. The 25% solution was a very strong skin irritant and healing of the dosage site was reported to be “delayed” (no further details provided). Weight loss was seen in all animals. The study authors suggest that this may indicate dermal absorption or may simply be attributed to a secondary consequence of the discomfort caused by the strong irritant properties of the material. No further information was provided. Although this study is of limited value, the results support the findings from the previous study.

In relation to glutaraldehyde, the data on the dermal toxicity show considerable variability. LD<sub>50</sub> values of 680 - 1432 mg/kg were reported in studies in rabbits exposed to 25-50% solutions. The cause of death was likely to have been a consequence of severe local damage to the skin and underlying tissue at the site of application. However, a study in rats exposed to a 50% glutaraldehyde solution gave an LD<sub>50</sub> value >2000 mg/kg, suggesting a possible species difference in response. Overall, the findings in the rat for glutaraldehyde and SDA suggest that these dialdehydes each have low systemic toxicity following dermal exposure. One reason might be the reactive nature of these substances causing them to bind to tissues at the site of application, rather than being available for absorption and systemic distribution.

#### **4.2.2 Studies in humans**

No data are available

#### **4.2.3 Summary of acute toxicity**

There are no human data on the effects of single exposure to SDA. There are no reliable animal studies of the acute inhalation toxicity of SDA. Acute oral toxicity studies in rats reveal that SDA is toxic by the oral route of exposure. Single dermal application of SDA in rats reveals that it is of low systemic toxicity by dermal exposure, with the only effects observed being those of local skin damage. Comparisons of the experimental data on SDA and glutaraldehyde reveal that they are qualitatively and quantitatively similar in relation to their acute oral and dermal toxicities. This supports the view that the acute inhalation toxicities of these two substances would also be broadly similar, suggesting that SDA (as is glutaraldehyde) is likely to be toxic on single inhalation exposure. For all exposure routes, adverse effects are likely to be largely a consequence of severe irritancy/inflammation at the site of contact.

### **4.3 Irritation**

#### **4.3.1 Studies in animals**

##### **Skin**

There are no specific skin irritation studies available. However, results from the acute dermal toxicity studies indicate that SDA does have the potential to induce skin damage at the site of administration. In one OECD-compliant single dermal dose study, erythema, oedema and punctate scabbing were present at the site of application of 2000 mg/kg of a 40% presumably aqueous solution (equivalent to 800 mg SDA/kg) (IBR Forschungs GmbH,

1989b). Scores were not reported. It is noted that the duration of exposure in this study (24 hours) is considerably longer than that required for a skin irritation study (4 hours). Also the amount of test compound that was applied is greater than the 500 mg/kg normally used. Hence, skin reactions at the site of application are likely to be more severe than the reactions that might have been seen for a 40% solution in a conventional skin irritation study.

Skin damage was also reported in an unpublished single dose dermal toxicity study conducted between 1958 and 1968 (species unspecified) (Kodak, 1958/68c). Aqueous solutions, with concentrations stated as ranging from 1 – 25% were applied simultaneously to three animals; irritation was apparently noted at all concentrations, with severity said to increase with dose. At the highest concentration, SDA appeared “highly irritant”, with delayed healing at the dosage site. No information was provided regarding the severity of reaction at lower doses. However, given the lack of detail in the study, coupled with the observation that a 1% solution was used for human patch testing in a sensitisation study (see section 4.4.2), these results are of questionable reliability.

Overall, these studies suggest that concentrated solutions of SDA would cause marked irritancy. For comparative purposes, glutaraldehyde is corrosive in skin irritation tests.

## **Eye**

In an unpublished study conducted between 1958 and 1968, one drop of a 25% solution of SDA administered to a rabbit’s eye was said to have caused corneal opacity and blindness (Kodak, 1958/68e). No further information was available. Based on this limited report and by analogy with glutaraldehyde (a severe eye irritant), it can be concluded that SDA is a severe eye irritant.

## **Respiratory Tract**

There are no studies on the potential irritancy of SDA to the respiratory tract. However, the results from the acute oral toxicity (gastrointestinal tract irritation), skin and eye irritation studies, coupled with the structural similarity to glutaraldehyde (a known respiratory tract irritant), suggest that SDA will also be a respiratory tract sensory irritant.

### **4.3.2 Studies in humans**

No data are available.

### **4.3.3 Summary of Irritation**

No human data are available. Studies in animals show that SDA solutions cause skin irritation, with severe effects at concentrations of 25 – 40%. 25% SDA also produced severe eye damage in rabbits. It seems likely from the pattern of evidence and by analogy with glutaraldehyde that undiluted SDA would be severely irritating to the skin and is also likely to have the potential to cause respiratory tract sensory irritation. From the information available, it is not possible to predict what the threshold airborne concentration of SDA would be for the elicitation of sensory irritation in humans.

## **4.4 Sensitisation**

### **4.4.1 Studies in animals**

## Skin

No conventional skin sensitisation studies have been conducted. In an unpublished study conducted between 1958 and 1968, of which very few details were reported, skin reactions described as “moderate sensitisation” were observed in all guinea pigs exposed to SDA (Kodak, 1958/68f). The authors reported that SDA elicited a stronger skin sensitisation reaction than formaldehyde, which was used in the control animals. No further detail was available. Given the limitations in the reporting of this study, with no details of the test procedures, for example whether or not sub-irritant concentrations of the test substances were used, this study cannot be considered to be reliable. Studies with glutaraldehyde in guinea pigs and mice have demonstrated that this substance is a skin sensitiser in these species. A potential for skin sensitisation with SDA might be predicted based on its chemical structure and by analogy with glutaraldehyde.

## Respiratory Tract

No data are available.

### 4.4.2 Studies in humans

#### Skin

In a study conducted during 1998 – 2000, the incidence of sensitisation to aldehydes, including SDA, was investigated in 388 health care workers (Krecisz & Kiece-Swierzczynska, 2000). The study group (354 women and 34 men) had a history of skin complaints in relation to the use of disinfecting agents. Patch tests were performed on all participants using standard allergen sets, which included tests with 1% formaldehyde in water, 0.2% glutaraldehyde in petroleum jelly, 1% glyoxal (a C<sub>2</sub> dialdehyde) in distilled water and 1% SDA in distilled water. A case of contact allergy was deemed to have been identified if a patient reacted to at least 1 of the challenges.

In total, 253 subjects showed at least 1 positive result, with positive results for the above aldehydes (taken together) in 92 workers. Of the 92 workers responding to aldehydes, 55 responded to formaldehyde, 40 to glutaraldehyde, 14 to glyoxal and 8 to SDA. Of the 92 who gave a positive result to aldehydes, 74 reacted exclusively to only one aldehyde, including 4 who reacted only to SDA. Eleven individuals responded to two aldehydes, one of whom responded to SDA and formaldehyde and 7 responded to three aldehydes, three of whom responded to SDA, glyoxal and formaldehyde (2) or SDA, glutaraldehyde and glyoxal (1).

These results suggest that SDA elicited skin reactions in a few individuals. However, as no information was provided on the proportion of the study group with previous occupational exposure to SDA-containing disinfectants, it is not clear if SDA had induced sensitisation in any of these individuals. Given that all participants were patch tested with the same concentration of SDA it seems unlikely that simple skin irritation was the cause of the 8 positive skin reactions. Cross-reactivity cannot be ruled out as accounting for some of the positive results in this study, but does not seem likely to have been a major confounder given the relatively small numbers of individuals responding to more than one aldehyde. Overall, it is difficult to draw any meaningful conclusions from this study, particularly as the previous exposure histories and current skin conditions of the participants were not stated.

Glutaraldehyde is known to elicit a strong skin sensitisation reaction in humans. Based on the chemical structure of SDA and comparison with glutaraldehyde, it might be reasonable

to predict that it would have the potential to cause skin sensitisation.

## Respiratory tract

There are no documented cases of occupational asthma associated with exposure to SDA. However, HSE has been unable to obtain any information on the extent of exposure to SDA in workers, and nor is there any information on the extent of current commercial use of SDA-containing products in UK hospitals. The lack of such information makes the absence of documented case-reports difficult to interpret. However, given the chemical and structural similarity to glutaraldehyde, a recognised asthmagen, the possibility must be acknowledged that SDA may also have the potential to induce asthma.

### 4.4.3 Summary of sensitisation

The sensitising properties of SDA have not been adequately investigated. Its chemical structure and similarity with glutaraldehyde might indicate that SDA is likely to have skin sensitising and asthmagenic potential.

## 4.5 Effects of repeated exposure

No studies have been conducted in either humans or experimental animals to determine the effects of repeated exposure to SDA. For glutaraldehyde, studies in rats and mice indicate that the upper respiratory tract is the key target site of toxicity following repeated inhalation exposure (see attached EH64 for glutaraldehyde for details of exposure-response relationships). Since the HSE review of glutaraldehyde was completed, a 2-year carcinogenicity study in rats and mice has become available (NTP, 1999). In this study, rats (50/sex/dose) were exposed to 0, 250, 500, or 750 ppb glutaraldehyde vapour by inhalation, 6 hours per day, 5 days per week. Mice (50/sex/dose) were exposed under the same regimen to 0, 62.5, 125 or 250 ppb. In both species, there was an exposure-related increase in the incidence and severity of nasal epithelial inflammation, with treatment-related effects seen at all concentrations tested. These results are consistent with those presented in the published EH64 for glutaraldehyde. Based on these findings with glutaraldehyde, it seems reasonable to predict that inflammation of the upper respiratory tract epithelium would also be the key effect of repeated inhalation exposure to SDA, although no precise conclusions can be drawn concerning the quantitative exposure-response relationships.

## 4.6 Mutagenicity

There are no genotoxicity data available for SDA, but based on read-across to glutaraldehyde, it would be expected to have a similar profile. Glutaraldehyde is a direct acting mutagen in bacterial and mammalian cells *in vitro* suggesting that SDA may also possess this property. However, the evidence from studies *in vivo* is somewhat patchy. Negative results have been obtained for glutaraldehyde in good-quality bone marrow cytogenetics, peripheral blood micronucleus and liver UDS assays *in vivo* (these studies are detailed in the attached glutaraldehyde EH64), providing reassurance that the genotoxic effects of glutaraldehyde *in vitro* are unlikely to be expressed *in vivo* at tissues distant from the site of contact. However, the potential for genotoxicity at the site of contact has not been examined. It is unclear from these findings whether or not SDA would have the potential to induce mutagenic effects *in vivo* in tissues at the site of contact. However, the overall pattern of results for this series of dialdehydes is not reassuring.

## 4.7 Carcinogenicity

No studies have been conducted in either humans or experimental animals to determine the carcinogenic potential of SDA. In view of this lack of data, it may be reasonable to base predictions on a read-across to glutaraldehyde. In an NTP carcinogenicity study there was no evidence of carcinogenic activity in rats exposed to up to 750 ppb glutaraldehyde vapour by inhalation, nor in mice exposed to up to 250 ppb; evidence of irritant damage of the nasal epithelia was present at all concentrations in both species (NTP, 1999). These findings provide some reassurance that SDA would also not exhibit carcinogenic activity on long-term repeated exposure.

#### 4.8 Toxicity to reproduction

No studies have been conducted in either humans or experimental animals to determine the reproductive effects of SDA. However, given that the systemic availability of SDA is likely to be very limited due to binding with tissues at the site of contact and rapid metabolism of any absorbed SDA, it is unlikely that there would be any significant exposure of the reproductive organs and developing foetus following occupational exposure to this substance. For the same reasons elimination in breast milk is not anticipated. Hence, there are no grounds to consider that SDA would be a reproductive toxicant. In support of this, there was no evidence from fertility and developmental toxicity studies with glutaraldehyde for effects on these endpoints.

**Table 3. Comparison of toxicity profiles of succinic dialdehyde and glutaraldehyde.**

ENDPOINT	SDA	GLUTARALDEHYDE
<b>Acute inhalation toxicity</b>	No reliable data	Toxic by inhalation: 4-hr LC <sub>50</sub> in rats (aerosol) 0.28 – 0.8mg.l <sup>-1</sup>
<b>Acute oral toxicity</b>	Toxic by ingestion: LD <sub>50</sub> = 68 mg SDA/kg	Toxic by ingestion: LD <sub>50</sub> = 111 – 633mg/kg (depending on dilution)
<b>Acute dermal toxicity</b>	Low systemic toxicity via the dermal route in rats:  No data in rabbits.	Low systemic toxicity via the dermal route in rats:  Acutely toxic in rabbits
<b>Skin irritation</b>	Severe skin irritant, possibly corrosive	Corrosive
<b>Eye irritation</b>	Very severe eye irritant	Corrosive
<b>Respiratory tract irritation</b>	No data	Sensory irritation reported in humans at 0.02 ppm.
<b>Skin sensitisation</b>	No reliable data	Positive results in animals and humans
<b>Respiratory sensitisation</b>	No data	Causes occupational asthma
<b>Repeated inhalation exposure</b>	No data	Mild nasal inflammation in mice at 0.0625 ppm, 6 hrs/dy
<b>Mutagenicity</b>	No data	Mutagenic <i>in vitro</i>  In vivo, not mutagenic in tissues distal

		to site of contact.
<b>Carcinogenicity</b>	No data	Negative results in 2-year inhalation study in rats and mice
<b>Reproductive toxicity</b>	No data	No effects on fertility or development in animal studies

## 5 References

Ballantyne B (1986). Glutaraldehyde: Review of toxicological studies and human health effects. Union Carbide company report.

BASF (1981). Internal company reports on acute oral and dermal studies with 50% glutaraldehyde dated 22/12/81 (in German).

HSE, (1997). Glutaraldehyde, Criteria document for an occupational exposure limit. EH65/32. HSE Books. ISBN 0-7176-1433-3

IBR Forschungs GmbH, (1989a). Acute oral toxicity in rats with 40% succinic dialdehyde. IBR project no. 1-4-506-89. Hanover, Germany.

IBR Forschungs GmbH, (1989b). Acute dermal toxicity in rats with 40% succinic dialdehyde. IBR project no. 1-4-507-89. Hanover, Germany.

Imaging Technology Group (ITG) (2001). Technical report 99-006, Cell biological applications of fluorescence microscopy: Specimen Preparation: Fixation, University of Illinois.

<http://www.itg.uiuc.edu/publications/techreports/99-006/fixation.htm>

Kodak (1958/68). Summary of Kodak archive toxicological data for Succinaldehyde (unpublished data).

Krecisz, B & Kiece-Swierczynska, M (2000). Allergic contact dermatitis from aldehydes in health care workers. A study based on data from the Nofer Institute of Occupational medicine, Kodz, Poland. *Przegląd Dermatologiczny*, **3**, 201 – 205.

NTP (1999). Toxicology and carcinogenesis studies of Glutaraldehyde in F 244/N and B6C3F1 mice (inhalation studies). NTP Technical Report Series TR 490.

<http://ntp-server.niehs.nih.gov/htdocs/LT-Studies/TR490.html>

Ohno K, Yasuhara K, Kawasaki Y *et al* (1991). Comparative studies on acute toxicity of glutaraldehyde using young and old rats. *Eisei Shikensho Hokoku*, **109**,92–97 (In Japanese, English summary).

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## SECTION 2. ORTHO-PHTHALALDEHYDE

### 1. SUMMARY

#### 1.1 Toxicity of ortho-phthalaldehyde

The only information on the effects of exposure to o-phthalaldehyde derives from a number of unpublished studies that were sponsored by the chemical manufacturer. There are no human data to inform on the health effects of exposure to o-phthalaldehyde.

No studies have been conducted to investigate the toxicokinetics of o-phthalaldehyde. Based on its chemical reactivity it would be predicted that o-phthalaldehyde would bind to tissues at the immediate site of contact, thereby limiting systemic uptake from occupationally relevant exposure routes.

There is no information on the acute inhalation toxicity of o-phthalaldehyde. However, its chemical reactivity and its acute oral toxicity suggest it is likely to be toxic on inhalation exposure. O-phthalaldehyde is acutely toxic by the oral route; an LD<sub>50</sub> of 121 mg/kg was reported in rats, with toxic effects largely restricted to the gastro-intestinal tract. O-phthalaldehyde is of low systemic toxicity via the dermal route of exposure, with an LD<sub>50</sub> of > 2000 mg/kg.

The irritant potential of o-phthalaldehyde has not been specifically investigated. However, severe eschar was observed at the site of application in all treated animals in the acute dermal study, indicating that it is corrosive. Given that extensive damage to the skin and gastro-intestinal tract was seen in the acute toxicity tests, it is likely that o-phthalaldehyde would also cause eye and respiratory tract irritation.

The sensitising properties of o-phthalaldehyde have not been adequately investigated. However, its chemical reactivity and analogy with other aldehydes suggest the possibility that it might have both skin sensitising and asthmagenic potential.

A limited number of studies into the mutagenic potential of o-phthalaldehyde have been conducted. Overall, the pattern of results indicates that it is an *in vitro* clastogen. *In vivo*, negative results were obtained in a rat bone marrow test. This result is of limited value due to the lack of evidence that o-phthalaldehyde reached the target tissue. However, it does suggest that o-phthalaldehyde would be unlikely to be mutagenic in tissues distal to the site of exposure. The potential for genotoxicity at the site of contact has not been examined. There remains a doubt therefore about the mutagenic potential of o-phthalaldehyde.

No carcinogenicity studies have been performed and given the uncertainties regarding the mutagenic potential, no predictions of the likely carcinogenic potential of o-phthalaldehyde can be made.

In an oral dosing developmental study in rats, delayed skeletal development was observed in the offspring from the top dose group (40 mg/kg) but this occurred in conjunction with severe maternal toxicity. These results do not indicate that o-phthalaldehyde is a developmental toxicant. No studies have been performed to determine potential effects on fertility. However, little or no systemic distribution to the reproductive organs would be expected to occur via occupationally relevant routes of exposure, and hence it might be predicted that o-phthalaldehyde would be unlikely to directly affect fertility.

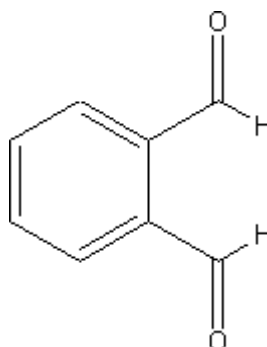
## 2 Introduction

O-phthalaldehyde is the active ingredient in a formulation marketed for use as a sterilant for endoscopy equipment. It is present in a "ready to use" preparation with the brand name "Cidex-opa®" containing 0.56% o-phthalaldehyde. The remaining 99.45% of this formulation is largely water; other unspecified substances, said to be "inert" are present at less than 1% on the suppliers' safety data sheet.

### 3 Identification

CAS No:	643-79-82
EINECS No.:	11-402-2
Molecular formula:	C <sub>8</sub> H <sub>6</sub> O <sub>2</sub>
Molecular weight:	134.1
Synonyms:	o-phthalic aldehyde o-phthaldialdehyde phthalaldehyde 1,2-benzenedicarboxaldehyde cidex-opa benzenedicarboxaldehyde phthalic dicarboxaldehyde
Physical state:	solid
Melting point:	56 °C
Boiling point:	not determined
Vapour pressure:	6.9 x 10 <sup>-1</sup> Pa at 21°C
Solubility:	soluble in water
Conversion factor:	1 ppm = 5.6 mg/m <sup>3</sup> at room temperature

Chemical structure:



### 4 Toxicokinetics and toxicology

#### 4.1 Toxicokinetics

No data are available on the toxicokinetics of o-phthalaldehyde (OPA) in animals or humans. Marketing information indicates that Cidex-opa® kills microorganisms very rapidly and effectively (within a contact time of 5-10 minutes), suggesting a high degree of chemical reactivity for OPA. Furthermore, it is known that as a group, aldehydes and dialdehydes are effective cross-linking agents. These observations suggest that following inhalation, dermal or oral exposure, OPA is likely to bind covalently to tissues at the site of contact, thereby limiting the potential for systemic uptake and distribution. However, some systemic uptake may occur across damaged tissue.

#### 4.2 Acute toxicity

##### 4.2.1 Studies in animals

## Inhalation

No data are available. The chemical reactivity and acute oral toxicity of OPA suggest it may be toxic on inhalation exposure.

## Oral

In an unpublished study, groups of rats (5/sex) received single oral doses of 25, 50, 100, 250 or 500 mg/kg OPA (99.8% pure; Reagen, 1988a). All treatment-related deaths occurred within 4 days of dosing and an LD<sub>50</sub> of 121 mg/kg was determined. The principal clinical observations were ataxia, decreased activity, diarrhoea, respiratory irregularity and urinary incontinence. These effects resolved by day 7 of the study in surviving animals. Gross necropsy findings for animals dosed with 50 mg/kg OPA and above indicated extensive damage to the stomach and intestines.

Similar clinical signs of acute oral toxicity were also observed in a rat chromosome aberration test ([section 4.6.2](#)) after administration of a single oral dose of 50 and 100 mg/kg OPA.

## Dermal

In an unpublished study, 2000 mg/kg OPA was applied to the shaved skin of rabbits (5/sex) under an occlusive dressing for 24 hours (Reagen, 1988b), followed by a 14 day observation period. There were no deaths or clear signs of systemic toxicity during the study. Dermal damage was seen; severe eschar was observed in all animals. No significant changes in body weights were observed during the study. Overall, as would be predicted from its chemical reactivity, the main effect of dermal exposure to OPA is skin damage at the site of contact.

### 4.2.2 Summary of acute toxicity

There are no data on the acute inhalation toxicity of OPA. Animal data reveal that it is acutely toxic via the oral route, with mortality being due to severe local damage to the gastro-intestinal tract. Its acute oral toxicity suggests it would also be toxic via single inhalation exposure, and would be likely to cause irritation and inflammation of the respiratory tract epithelium. OPA was of low systemic toxicity in an acute dermal toxicity test in rabbits, with the only effects observed being local skin damage at the site of application.

## 4.3 Irritation

### 4.3.1 Studies in animals

#### Skin

There are no skin irritation studies available. However, based on the results from the acute dermal toxicity study in rabbits where eschar was seen in all animals, OPA should be regarded as corrosive.

#### Eye

There are no data available. However, since OPA causes local damage to the skin and gastro-intestinal tract, and given that other aldehydes are known eye irritants, it is

reasonable to predict that OPA would be an eye irritant.

## Respiratory tract

There are no studies on the irritancy of OPA to the respiratory tract, although the chemically reactive nature of the molecule, and the fact that other aldehydes and dialdehydes are known respiratory tract irritants, suggests that OPA would have the potential to cause inflammation and sensory irritation of the respiratory tract.

### 4.3.2 Summary of irritation

Although the skin irritation potential of OPA has not been formally investigated, the findings from an acute dermal study in rabbits indicate that it should be regarded as corrosive. It is predicted that OPA is likely to be a severe eye irritant and, if inhaled, would cause sensory irritation and inflammation in the respiratory tract.

## 4.4 Sensitisation

### 4.4.1 Studies in animals

#### Skin

There are no studies on OPA. However, a guinea pig Buehler study has been conducted on the Cidex-opa® preparation which contains 0.56% OPA (Lilja, 1988d). Negative results were obtained in this study, but HSE considers that the test was not sufficiently rigorous, mainly because no evidence for skin irritation was reported for the induction phase, implying that sub-irritant concentrations were used. Also, OECD guidelines require that 10 vehicle control animals should have been used, whereas the study only employed four such animals. While not a severe criticism, it adds to the impression that this was not a rigorous study.

Overall, HSE feels that no firm conclusions can be drawn concerning the skin sensitising potential of OPA from this study. It might therefore be helpful to explore what is known about structurally similar chemicals. Accordingly, it is well documented that alkyl aldehydes such as formaldehyde and glutaraldehyde are skin sensitisers, and that dialdehydes such as glutaraldehyde are more potent than monoaldehydes such as formaldehyde (Hilton et al., 1998).

However, it is noted that the aldehyde groups on OPA are not linked to an alkyl chain such as is the case with glutaraldehyde. Rather, they are attached to a benzene ring. Benzaldehyde, like OPA, is an aryl aldehyde that differs in having only one aldehyde group directly attached to a benzene ring, rather than the two in OPA. It has been recently reported that benzaldehyde gave negative results in the local lymph node assay (Patlewicz *et al.*, 2001). This suggests a lack of skin sensitisation potential for this substance. One reason for this lack of activity may be that the aldehyde group in benzaldehyde is stabilised by the resonance on the benzene ring. HSE has been unable to find any references to benzaldehyde causing skin allergy in humans to help inform on this issue.

These observations might suggest that the sensitising potential of OPA could lie somewhere between that of glutaraldehyde and benzaldehyde. However, it is recognised that low molecular weight sensitisers must be chemically reactive, in order to covalently bind to tissue proteins thus forming an immunologically active hapten. In this regard, it seems only logical to assume that OPA must be very reactive, given that Cidex-opa® contains only 0.56% OPA, and yet this formulation is claimed to kill most microorganisms

within 5 to 12 minutes of contact.

Thus while no hard evidence is available on the skin sensitisation potential of OPA, given that it must be chemically reactive, able to rapidly covalently bind to biological molecules, and given that other dialdehydes are known sensitisers, it could be predicted that OPA might have sensitising potential.

### **Respiratory tract**

No experimental data or case reports of occupational asthma associated with OPA are available. However, HSE has no information on the extent of use or levels of occupational exposure to OPA, and so the lack of documented case-reports of asthma associated with this substance is difficult to interpret. However, as discussed above in the skin sensitisation section, it might be reasonably predicted that OPA would have some sensitising potential, and hence might have the potential to cause occupational asthma.

#### **4.4.2 Summary of sensitisation**

There are no experimental data or human case reports to inform on the skin or respiratory sensitisation potential of OPA. Based on the known asthmagenic potential of glutaraldehyde, which is also a dialdehyde, and based on the chemical reactivity of OPA, it seems possible that OPA could have some potential to cause skin sensitisation and asthma.

### **4.5 Effects of repeated exposure**

#### **4.5.1 Studies in animals**

##### **Respiratory tract**

No studies have been conducted in experimental animals to determine the effects of repeated inhalation exposure to OPA. Given that OPA causes site of contact irritation on oral and dermal dosing, it is predicted that the respiratory tract epithelium would be the key target of toxicity for inhaled OPA, but it is not possible to draw any conclusions about dose-response relationships.

##### **Oral**

A study has been reported in which rats (10/sex for the low and mid dose groups and 15/sex for the control and high dose groups) were dosed with OPA daily by oral gavage at 0, 0.5, 5 and 50 mg/kg/day for 90 days (Markiewicz, 1989).

In females, 5 of the top dose group rats died within the first 10 days. Due to the high rate of mortality at this concentration, the top dose was reduced to 25 mg/kg/d for female rats from day 11 onwards. Top dose male rats continued to receive 50 mg/kg/d.

Treatment-related mortality occurred in top dose animals only, with deaths occurring in 12/15 males and 10/15 females by the end of the study. In decedents, clinical signs and pathological findings indicated severe damage to the gastro-intestinal tract. No deaths occurred in the mid and low dose group animals.

Haematology revealed that in top dose rats there were increases in white blood cells; total leukocyte counts, segmented neutrophils and monocytes were significantly increased in

males, and total leukocyte and neutrophils were increased in females. These are indicative of an inflammatory condition. No treatment-related haematological effects were observed for rats exposed to the mid and low doses.

Clinical chemistry revealed decreases in total protein (20 %), albumin (22 %) and globulin levels (23 %) in high-dose male rats. For high dose females and all other treatment groups no dose-related effects were observed. The clinical chemistry changes reflect the consequences of severe gastro-intestinal tract inflammation with associated oedema and plasma exudates. There were no treatment-related changes observed in the urinalysis or ocular examination.

In top dose animals there were reductions in absolute organ weights in the thymus, heart, kidney and testes, but these changes were seen in conjunction with severe debility and body weight loss, and hence cannot be regarded as direct effects of OPA on these organs.

## **Dermal**

No data are available. From the general picture available it is predicted that repeated dermal exposure to OPA would cause local skin damage.

### **4.5.2 Summary of repeated exposure**

There are no data to inform on the repeated exposure toxicity of OPA by inhalation or by dermal exposure. For both exposure routes, local site of contact irritant effects would be predicted to occur. A study in rats involving repeated oral dosing with OPA predictably revealed severe local damage to the gastro-intestinal tract.

## **4.6 Mutagenicity**

### **4.6.1 Studies *in vitro***

#### **Studies in bacteria**

In an unpublished study conducted according to GLP and OECD guidelines, OPA (99% pure) in dimethylsulphoxide was tested in a plate incorporation Ames test (Lawlor and Wagner, 1986). *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA102 and TA104 were incubated for 48h at OPA concentrations of 0.4, 2, 10, 30 and 60 µg/ml with metabolic activation and 0.08, 0.4, 2, 10 and 20 µg/ml without metabolic activation. For strain TA102 the top concentration tested was increased to 120 µg/ml with metabolic activation. Cytotoxicity was observed with all strains at the top concentrations with and without metabolic activation. No increase in the number of revertants was observed for any strains either with or without metabolic activation.

#### **Studies in mammalian cells**

In a briefly reported study, OPA (99.7% pure) was tested for the potential to induce chromosome aberrations in Chinese Hamster Ovary cells (CHO; unreferenced summary report provided by Johnson & Johnson). Duplicate cultures of the cells were exposed to OPA in distilled water at concentrations of 0.35, 0.7, 1.30, 2.5 and 5 µg/ml for 16 hours without metabolic activation and 2 hours with metabolic activation. Both cultures were harvested after 16 hours. At each concentration the number of chromatid and chromosome aberrations were scored in 100 metaphases per treatment and the mitotic index determined in 500 cells per replicate. Cytotoxicity (assessed by a reduction in the mitotic index of the

cells) was observed at 5 µg/ml both with and without metabolic activation. A dose-related increase in the number of aberrations (no data given) was observed in cultures treated without metabolic activation at concentrations of 1.3, 2.5 and 5 µg/ml. For cultures incubated with metabolic activation an increase in the number of aberrations was seen at 5 µg/ml only (no data given). This test was not independently repeated and no further details were given in the report, but it indicates that OPA induces chromosome aberrations in cultured mammalian cells.

In an unpublished study conducted according to GLP and OECD guidelines (1988), the potential for OPA to induce sister chromatid exchanges (SCEs) in CHO cells was determined (Putnam and Morris, 1988). Cells were incubated with OPA (99% pure) in distilled water at concentrations of 0, 0.4, 0.8, 1.5 and 3 µg/ml without metabolic activation for 26 hours and with metabolic activation for 2 hours (with a further 24 hour incubation without the test substance and metabolic activation). Each concentration was tested in duplicate and cytotoxicity (assessed by cell cycle delay) was observed at the highest concentrations. A dose-related increase in SCEs was observed for cells treated with OPA both with and without metabolic activation. This test was only performed once; however it demonstrates that OPA produced a positive result for the induction of SCEs both in the presence and absence of metabolic activation in CHO cells.

In an unpublished study conducted to GLP and OECD guidelines (1988), the potential for OPA to induce mutation at the thymidine kinase (TK) locus in mouse lymphoma cells was investigated (Harbell, 1988). Cells were incubated with OPA (99% purity) in distilled water for 5 hours without metabolic activation at 1, 5, 10, 15 and 20 µg/ml and with 3, 9, 16, 23 and 30 µg/ml with metabolic activation (5 plates per concentration). The same exposure concentrations were used for the independently repeated test. Relative cell survival was approximately 20 - 25% at the top dose both with and without activation in the first experiment and approximately 1% in the second experiment. There was no dose-related increase in the number of mutant frequencies in either experiment. Positive and negative controls gave results in the expected region. Therefore, in this test system, OPA did not induce gene mutation in mammalian cells.

In an unpublished study conducted to GLP and which broadly follows the current OECD guidelines, OPA (99.7% purity) was tested for the potential to induce unscheduled DNA synthesis in rat hepatocytes (Curren, 1988). Triplicate cultures obtained from Fischer 344 rats were incubated with OPA in distilled water at concentrations of 0, 0.5, 1.5, 5, 10 and 15 µg/ml for 18 – 20 hours and DNA synthesis was measured by the incorporation of tritiated thymidine using autoradiography. Fifty metaphases per replicate (150 per dose) were scored for the presence of grains in the nucleus and cytoplasm. Cytotoxicity was observed by microscopic examination (no further details were given) at concentrations of 10 and 15 µg/ml, although cytotoxicity determined by the release of lactic acid dehydrogenase was not seen. There was no dose-related increase in the mean number of net nuclear grains. Positive and negative controls gave expected results. Overall, a negative result was obtained, but this was not confirmed by conducting an independent repeat of this test.

#### **4.6.2 Studies *in vivo***

In an unpublished mammalian bone marrow chromosome aberration test that was conducted to GLP and OECD guidelines (1988), OPA (99.7% pure) in distilled water was administered to rats (5/sex/dose) by gavage in a single dose of 0, 10, 50 or 100 mg/kg (Putnam, 1989). Seven, 24 and 48 hours after administration, the presence of chromosome aberrations was assessed in 150 metaphases per animal. The positive control (5 rats/sex) received cyclophosphamide at 25 mg/kg and the animals were sacrificed 24h after administration. Cytotoxicity in the bone marrow was measured by determining the mitotic

index in 500 cells per animal. Mortality was observed in 5/20 males and 7/20 females (including animals dosed as a reserve) at 100 mg/kg and in 1/15 males and 1/15 females dosed with 50 mg/kg. Clinical signs of toxicity were observed in rats receiving 50 (1/5 males and 1/5 females) and 100 mg/kg (the majority of animals) resulting in lethargy, laboured breathing, prostration, piloerection, crusty nose or eyes, clear secretions around nose or mouth and gasping. Assessment of the bone marrow at doses of 50 and 100 mg/kg was done in 5 animals/sex/dose. The number cells with chromosome aberrations observed 24 hours after treatment was 0, 0, 0, and 1 for males and 2, 0, 1 and 0 for females following treatment with 0, 10, 50 and 100 mg/kg respectively. Forty-eight hours after treatment number of cells with chromosome aberrations were 0, 0, 4 and 1 for males and 0, 1, 0 and 1 for females treated with 0, 10, 50 and 100 mg/kg. The mitotic index was unchanged for all treatments providing no evidence for bone marrow toxicity.

This study gives some reassurance that the genotoxic effects of OPA observed *in vitro* are unlikely to be expressed *in vivo* at tissues distal to the site of contact. However, according to the Committee on Mutagenicity in Food, Consumer Products and the Environment (COM, 2000) negative results in at least two somatic cell tests are required before sufficient reassurance for the absence of *in vivo* mutagenic activity can be achieved. The potential for genotoxicity at the site of contact has not been examined.

#### 4.6.3 Summary of mutagenicity

The mutagenic potential of OPA has not been fully investigated. Positive results were reported in a chromosome aberration and sister chromatid exchange assay in mammalian cells, indicating that OPA has clastogenic potential *in vitro*. However, negative results were reported in bacterial cells, and in mammalian cell tests for unscheduled DNA synthesis and cell gene mutation. Overall, OPA should be regarded as an *in vitro* mutagen.

In somatic cells *in vivo* there is only a rat bone marrow chromosome aberration test available. The result was negative, but is of limited value due to the lack of evidence that OPA reached the target tissue. It provides reassurance that OPA would be unlikely to cause genotoxicity in tissues distal to the site of administration, but does not inform on the potential for genotoxicity in tissues at the immediate site of contact.

#### 4.7 Carcinogenicity

No carcinogenicity studies have been conducted. From the available toxicological profile, noting in particular the irritancy and uncertainties regarding the *in vivo* mutagenic potential, no confident predictions of the likely carcinogenic potential of OPA can be made.

#### 4.8 Toxicity to reproduction

##### 4.8.1 Studies in animals

##### Fertility studies

No studies investigating the potential effects of OPA on fertility have been identified. Reduced testes weight was observed in a 90-day oral gavage study but as this occurred in the presence of marked debility this cannot be taken as evidence for a specific effect on the gonads. Given that the systemic absorption of OPA is likely to be very limited due to binding with tissues at the site of contact, it is unlikely that there would be any significant exposure of the reproductive organs following occupational exposure. Hence, there are no grounds to consider that OPA would be a reproductive toxicant.

## Developmental studies

In an unpublished study conducted to GLP, the developmental toxicity of OPA in rats was investigated (Morseth, 1989). Mated female rats (25/dose) were dosed with 0, 10, 20 or 40 mg/kg of OPA in distilled water from gestation day 6 to 15. All animals were confirmed pregnant except for two control and two high dose females. On gestational day 20 the pregnant females were sacrificed and the litters delivered by caesarean section. Gross necropsy was performed on the dams and the uterine contents examined. Fetuses were weighed, sexed and examined for external, soft tissue and skeletal abnormalities.

Among the dams, treatment-related deaths were observed in 5 pregnant dams at 10 mg/kg and 10 pregnant and 1 non-pregnant dam at 40 mg/kg. Pathological changes in these animals were moderate to severe distended stomach and/or intestines, depressions in stomach, mottled liver, foci on liver and dark lungs. Clinical signs of toxicity (similar to those observed in the 90 day repeat dose study) were seen in all treated groups, the severity of which was dose-related. Apparently, body weights and water consumption in the high dose group were significantly lower than controls (data not given) and mid and high dose dams showed significantly lower food consumption compared to controls (data not given). There were no changes in the number of live or dead fetuses, corpora lutea, resorptions or fetal weight at any dose and no changes found on external examination or examination of the soft tissue of the fetuses. Examination of the skeleton of the fetuses showed an increase at top dose in the occurrence of unossified vertebral centrum (1, 0.5, 0 and 9% for 0, 10, 20 and 40 mg/kg respectively), unossified or incompletely ossified sternbrae (34, 36, 28 and 94%) and bent and/or wavy ribs (0.6, 0, 0, and 9%), all indicative of delayed development.

In conclusion, delayed skeletal development was observed in the 40 mg/kg treated group. However, at this dose significant maternal toxicity, a decrease in maternal body weight, food and water consumption and death were observed. The minor skeletal effects observed in the fetus at this dose are likely to be a result of maternal toxicity and do not indicate evidence for specific developmental toxicity.

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## 5 References

COM (2000) Guidance on a strategy for testing of chemicals for mutagenicity. Department of Health. 23094 1P 0.5K January 01 (CWP).

Curren, R. D. (1988) Unscheduled DNA synthesis in rat primary hepatocytes. Microbiological Associates, Bethesda, USA. Unpublished study report number T8157.380.

Harbell, J. H. (1988) CHO/HGPRT Mutation assay, with confirmation. Microbiological Associates, Bethesda, USA Unpublished study number T8241.332001.

Hilton J, Dearman RJ, Harvey P et al., (1998) Estimation of relative skin sensitising potency using the local lymph node assay: a comparison of formaldehyde with glutaraldehyde. *Amer J Contact Dermatitis* **9**: 29-33.

Lawlor, T. E. and Wagner, V. O. (1986) Salmonella/mammalian-microsome plate incorporation mutagenicity assay (Ames test). Microbiological Associates, Bethesda, USA. Unpublished study number T 5203.501027.

Markiewicz, V. R. (1989) Sub-chronic toxicity study in rats with o-phthalaldehyde. Hazleton Laboratories, Vienna, USA. Unpublished study number 2256-116.

Morseth, S. L. (1989) Rat teratology study. Hazleton Laboratories, Vienna, USA. Unpublished study number 2256-117.

Patlewicz G, Basketter DA, Smith CK et al., (2001) Skin sensitisation structure-activity relationships for aldehydes. *Contact Dermatitis* **44**: 331-336.

Putnam, D. L. (1989) Acute *in vivo* cytogenetics assay in rats, Bethesda, USA. Microbiological Associates. Unpublished study number T8241.105007.

Putnam, D. L. and Morris, M. M. (1988) Sister-chromatid exchange assay in Chinese hamster ovary cells. Microbiological Associates, Bethesda, USA. Unpublished study report number T8241.334.

Reagen, E. L. (1988a) Acute oral toxicity study of 806-77-1 in Sprague-Dawley rats. Food and Drug Research Laboratories, Waverly, USA. Unpublished study number 87.3140.001.

Reagen, E. L. (1988b) Acute dermal toxicity study of 806-77-1 in New Zealand White rabbits. Food and Drug Research Laboratories, Waverly, USA. Unpublished study number 87.3140.002.



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APPENDIX 2  
(para 8)

PERACETIC ACID

Paper Number: WATCH/19/2002  
Meeting Date: 19 September 2002

**HEALTH AND SAFETY COMMISSION**  
**ADVISORY COMMITTEE ON TOXIC SUBSTANCES**  
**WATCH SUB-COMMITTEE**  
**PERACETIC ACID**

*Issue*

1. Toxicological hazard profile for peracetic acid, including dose-response characterisation for the key potential health effects and prediction/identification of the highest overall no-effect level for human exposure.

**Timing**

2. A position from WATCH is desired at the September 2002 meeting

**Recommendation**

3. WATCH is invited to respond to the actions in [paragraph 13](#).

**Background**

4. Peracetic acid is a corrosive substance with major uses in the UK in chemical synthesis, disinfection and bleaching processes. It is widely used in the food industry and in the agricultural sector. Commercial formulations of peracetic acid are also used as an alternative to glutaraldehyde-containing products for the sterilisation of medical endoscopy equipment. In this regard, this assessment of peracetic acid sits alongside a separate technical package on two other such alternatives (succinic dialdehyde and ortho-phthalaldehyde) for consideration at this WATCH meeting (WATCH/20/2002). The views of WATCH in relation to all three "alternative" substances will be used to help provide a response to HSE's FOD in relation to alternatives to glutaraldehyde (see further discussion in WATCH/20/2002).

5. The HSE review of the toxicology of peracetic acid takes the form of a Bridging Document, based on a recent review document produced by the European Centre for Ecotoxicology and Toxicology (ECETOC). Overall, the documentation provided with this WATCH cover paper comprises:

Annex 1: HSE toxicology bridging document

## [Annex 2: Draft EH64-style summary document](#)

6. There is no current UK occupational exposure limit for peracetic acid in EH40 and there are challenging technical issues surrounding the method of analysis of workplace air samples and the assessment of contemporary levels of occupational exposure. HSE is not yet in a position to bring to WATCH a conventional package containing exposure and risk assessments and proposed risk management measures. The ongoing project to consider modifications to the UK OEL Framework and the plan for any agreed changes to be worked up during 2003 for introduction in 2004 suggests to HSE that this is not the appropriate time to seek to progress the development of an OEL for peracetic acid under the existing framework and system. However, the views of WATCH on the hazard profile will be available for use within any new OEL framework that emerges in the near future.

### **Argument**

#### Health hazardsL

7. Peracetic acid is a corrosive liquid for which the key health effects from inhalation exposure to the vapour and/or aerosol are those of sensory irritation and inflammation in the eyes and respiratory tract. These are the key concerns for occupational exposure to peracetic acid. However, the available data on these aspects is limited. Sensory irritation symptoms can only really be explored in humans; unfortunately, for peracetic acid the available data of this type derives from a small number of brief unpublished "in-house" occupational hygiene reports. These reports include the authors' comments or judgements/predictions on subjective symptoms based on their experiences during air-sampling activities. These reports are detailed in the attached HSE Bridging Document, and are cited in a table in the ECETOC review (p 103).

8. HSE is concerned that the information contained in these reports does not seem sufficient to provide a reliable indication of the exposure-response relationships for sensory irritation, or indeed to indicate where the threshold for sensory irritation might lie. WATCH is asked to consider, based on the information presented in this technical package, whether or not it would agree with this assessment.

9. A fuller picture of the available toxicity information on peracetic acid is given in the attached EH-64 style toxicology profile ([Annex 2](#)). It can be seen from this that there are no useful data concerning the effects of repeated inhalation exposure to peracetic acid, either from animal or human studies. HSE views this as an additional concern with regard to the adequacy of understanding of the toxicology profile of peracetic acid.

10. There are no reports of occupational asthma associated with peracetic acid, and it is not predicted to have sensitising properties. The position as regards other potential health endpoints is given in Annex 2. WATCH is asked to form its view of the overall toxicity profile of peracetic acid and to address the question of whether or not it feels able, with confidence, to identify the highest level of exposure (in terms of short-term peaks and/or workshift averages) at which no health effects would occur on single or repeated exposure.

### **Consultation**

11. No consultation beyond HSE has been undertaken at this stage. HSE has informed the Department of Health and the Scottish and Welsh offices that this review is being undertaken.

### **European Implications**

12. There are no European implications for this work.

### Action

13. WATCH is asked to consider the attached documentation and to:

- i Agree a position with respect to the toxicological hazards of peracetic acid.
- ii Give its view on whether, from the information presented in the package attached to this cover paper, it is possible to determine or predict, with reasonable confidence, where the threshold for sensory irritation in humans might lie.
- iii Address the question of whether or not it feels able, with confidence, to identify the highest level of exposure (in terms of short-term peaks and/or workshift averages) at which no health effects would occur on single or repeated exposure.

## TOXICOLOGY BRIDGING DOCUMENT: PERACETIC ACID

### Introduction

Peracetic acid is a corrosive liquid for which the key identified health effects from inhalation exposure to the vapour and/or aerosol are those of sensory irritation and inflammation in tissues at the immediate site of contact (eyes and respiratory tract). A comprehensive review of published and unpublished studies (up to the year 2000) on peracetic acid has been produced by the European Centre for Ecotoxicology and Toxicology (ECETOC, JACC No 40, 2001). This has been used the basis for this Bridging Document. In this Bridging Document HSE has commented below on the key areas emerging from the ECETOC review and has added a summary of a more recently published Alarie assay (Gagnaire *et al* 2002) A summary of the overall toxicological profile of peracetic acid is given in the draft EH64 entry accompanying this WATCH package ([Annex 2](#)).

### Background note on commercially available formulations of peracetic acid

As is more fully described in the ECETOC document, peracetic acid is always in chemical equilibrium with acetic acid, hydrogen peroxide and water and dilution may result in changed equilibria. It is also possible to prepare peracetic acid solutions with the same peracetic acid concentrations but containing different concentrations of co-formulants. Thus, workplace exposures are likely to be to imprecisely characterised mixtures of peracetic acid, acetic acid and hydrogen peroxide.

### Animal Data

The available animal data published up to 2000 is presented in the ECETOC review. Some comment is merited on the repeated inhalation exposure studies in animals (pages 81-87 of the ECETOC review), as often such data are of key importance for occupational risk assessment and standard-setting. Most studies have been conducted in mice and guinea pigs, although a non-standard study in calves and pigs has also been reported.

In HSE's opinion there are severe limitations on the quality and/or usefulness of the available studies. Firstly, many of them did not include histopathological examination of the upper respiratory tract, which is anticipated to be a key target site for toxicity. Secondly, the exposure concentrations achieved were estimated, but were not confirmed by analytical measurement; related to this point, the relative proportions of hydrogen peroxide, acetic

acid and peracetic acid in the exposure atmospheres are uncertain. Furthermore, a general feature of these studies is that the daily exposure durations were short (typically 5-30 minutes, once or twice a day), usually to fairly high estimated concentrations, 50-1125 mg.m<sup>-3</sup>. In addition, the quality of some of the individual studies is doubtful on other grounds; for example, one of the studies (Heinz *et al* 1981) is cited in the ECETOC review as having a No-Observed Effect Concentration of 281 mg.m<sup>-3</sup> in mice. However, HSE's inspection of the study report reveals that the histopathological findings were not clearly reported; hence HSE considers that the reported results of this study are unreliable. In another case, intercurrent infection causing liver granuloma was claimed in a study in mice and guinea pigs (Heinz and Natterman 1984).

Unfortunately, no repeated inhalation exposure studies are available that followed standard regulatory protocols (6-8 hours daily duration) to occupationally relevant exposure concentrations of peracetic acid. Due to the limitations in the available studies, a reliable and thorough picture cannot be assembled for the exposure-response relationship for repeated inhalation exposure in experimental animals.

### **Animal data not covered in the ECETOC Review**

In a well-conducted Alarie assay groups of eight male mice/concentration were exposed nose-only to four different test atmospheres for 60 minutes (Gagnaire *et al*, 2002). Animals were exposed to (i) peracetic acid-only at concentrations from 5.6 to 76 mg.m<sup>-3</sup>; (ii) a formulation containing 39% peracetic acid at total peracetic acid concentrations from 5 to 36.6 mg.m<sup>-3</sup>, (iii) to hydrogen peroxide at concentrations from 35 to 295 mg.m<sup>-3</sup> or (iv) to acetic acid at concentrations from 140 to 960 mg.m<sup>-3</sup>.

The test atmosphere compositions were all independently measured. The peracetic acid-only atmosphere was generated by buffering a commercial peracetic acid preparation in pH 7 phosphate buffer. Respiration rate was monitored by use of whole-body plethysmographs, before, during and post-exposure. Histopathological examination was not performed; such examinations are not routinely conducted in Alarie assays.

The RD<sub>50</sub> values (concentrations producing a 50% decrease in the respiratory rate) were 17, 12, 157 and 560 mg.m<sup>-3</sup> for peracetic acid-only, the peracetic acid formulation, hydrogen peroxide and acetic acid respectively. These data show a good consistency of response for the two separately generated peracetic acid atmospheres. Given that this was a very well-reported modern study, the results appear reliable and indicate that peracetic acid is more potent at causing respiratory tract irritation than either acetic acid or hydrogen peroxide. The results also suggest that the peracetic acid component may be predominantly responsible for the respiratory tract irritation caused by peracetic acid formulations.

### **Human data**

Several reports referring to the sensory irritant effects of peracetic acid are cited in the ECETOC review (page 103). Most of these are unpublished, and where possible, HSE has obtained these reports for a more detailed appraisal. It is noted that the unpublished studies were not designed to investigate the human health effects of peracetic acid, but are brief "in-house" occupational hygiene reports detailing air sampling results, in which passing comments have been made on the subjective irritant responses of the analysts involved. Overall, HSE feels that these reports do not yield any reliable information concerning the sensory irritant potential of peracetic acid. However, further details are outlined below given

that the ECETOC review might convey a different impression.

A brief unpublished report of a workplace air sampling exercise in a chemical plant is available (McDonagh 1997 ECETOC review p103). It can be gleaned from this report that a number of short-term air samples were taken over a 3-hour period in a plant in which distilled peracetic acid is used as the main reactant in caprolactone monomer production. The aim was to determine the airborne concentrations of peracetic acid vapour present in the two distillation houses during normal operation. The sampling methods were not described, but HSE surmises from the report that they involved background, rather than personal, breathing-zone sampling. The analytical method for measuring peracetic acid was based on total peroxides, rather than being specific for peracetic acid. However, the contribution made by hydrogen peroxide was judged to be small for the following reasons; the authors calculated that any vapour present would contain over 95% peracetic acid, as peracetic acid has a much greater vapour pressure than hydrogen peroxide. Furthermore, peracetic acid was present at 38% in the liquid state whereas hydrogen peroxide was only present at 17%. Thus, although the analytical method is not specific for peracetic acid, under these circumstances, it was considered to provide a reasonable estimate of the peracetic acid concentration.

Eight air samples, each of 0.5 minutes duration, were taken in the two still houses (one each on the ground floor, first, second and third floors). Also, one sample of 11 minutes duration was taken for general plant exposure. Thus, the "total duration" of sampling in the still houses over this 3-hour period was 4 minutes (8 samples of 30 seconds duration). In one of the still houses, the ground floor vapour concentration of 0.4 ppm (0.5 minute sample), was said not to cause any immediate irritation, but was judged likely to be "unpleasant" over an extended period. The first floor vapour concentrations in the still houses were 0.13 and 0.17 ppm; the authors described these exposures as "tolerable" and "not unpleasant", and did not cause any lacrimatory effects (it appears as though the odour was detectable at these levels). Airborne concentrations on the upper floors had no detectable odour, and were assigned "worst-case" values of 0.05 ppm (presumably actual levels were below the limits of detection).

Overall, HSE feels that this report is of very limited value in terms of contributing towards an understanding of the exposure-response relationship for sensory irritation from exposure to peracetic acid. The ECETOC review has presented these results as indicating that exposure to a vapour concentration of peracetic acid of 0.13 - 0.16 ppm would be tolerable for up to 3 hours, but in the opinion of HSE, this conclusion cannot be reliably drawn from the data available.

In a table in the ECETOC review (page 103) a reference to an unpublished report by Simms (1995) is given, claiming that exposure to  $0.3 \text{ mg.m}^{-3}$  (0.1 ppm) of peracetic acid produced no symptoms of runny eyes or nose. HSE has obtained this unpublished reference, and concludes that little reliance can be placed on it. This brief report describes the results of an air sampling exercise in a hospital operating theatre following concerns raised by staff over "peroxygen levels" in the working atmosphere. Air samples were taken in a room in which a bath containing a fresh sample of a commercial formulation of peracetic acid was present. Samples were of 10-minutes duration, and were taken at different heights above the bath, and at the entry to the theatre, 9 feet away from the bath. The analytical method was for hydrogen peroxide and total oxidants, but it is unclear from the report what the reported values represent (it seems that all values given are for hydrogen peroxide). The three workers taking the atmospheric samples reported no symptoms of irritation during their 3-hour presence in the room. However, it cannot be determined from the report what their personal exposures to peracetic acid vapour would have been.

The ECETOC review (page 103) also cites a reference by Harvey 1992. This is also an unpublished brief report of an air sampling exercise in a hospital in which peracetic acid was used for endoscopy sterilisation. Ten litres of a peracetic acid formulation (containing 0.35% peracetic acid) were placed in a bath and 10-minute air samples were taken hourly for 5-hours followed by a 24-hour sample. No information was provided regarding the siting of samplers. Peracetic acid was measured by a quantitative technique based on the oxidation of iodide to iodine. It is possible that hydrogen peroxide could interfere with this assay and the reported peracetic acid exposures may therefore be overestimates. The limit of detection of atmospheric peracetic acid was not stated. The analysts taking the air samples reported no appreciable odour associated with an estimated airborne peracetic acid concentration of " $<0.5 \text{ mg.m}^{-3}$ ". No useful information concerning the sensory irritant potential of peracetic acid can be gleaned from this report.

The ECETOC review cites another unpublished report by Fraser and Thorbison (1986). This report describes a series of "fogging trials" in a chicken house using a 1:20 dilution of a commercial peracetic acid formulation (containing 4% peracetic acid). The diluted formulation was poured into the fogger and air measurements were taken at different distances from the fogger throughout the shed. Symptoms (ranging from extreme discomfort to no discomfort) were reported at these different distances. However, no information is provided in the report concerning the numbers of individuals exposed (possibly it was either one or both of the two authors of the study but this is unclear). It is also unclear what the durations of exposure were at the different distances from the fogger. A further difficulty with this report is that the exposure levels were reported as hydrogen peroxide, and no estimates of the likely peracetic acid levels were given. No useful conclusions about the quantitative exposure-response relationships for the sensory irritant effects of peracetic acid can be drawn from this report.

Schaffernicht and Muller (1998, ECETOC review p104) measured air concentrations of peracetic acid at 45 workstations in one hospital. Staff at the hospital had complained of a range of symptoms, including irritation of the eyes and nasal and pharyngeal mucous membranes, as well as reddening and itching of the skin on the hands and face. No information on the severity or prevalence of the symptoms among the 150 staff was provided. Air samples were said to be taken from breathing zone height and were reported as 8-hour TWA values. Peracetic acid was measured by a quantitative technique based on the oxidation of iodide to iodine. It is possible that hydrogen peroxide could interfere with this assay and the reported peracetic acid exposures may therefore be overestimates. It was not reported whether peracetic acid was present as a vapour and/or as an aerosol.

The measured concentrations varied from  $0.005 \text{ mg.m}^{-3}$  (the detection limit) to  $1.84 \text{ mg.m}^{-3}$ , with 60%  $<0.1 \text{ mg.m}^{-3}$  and only 5%  $>1.0 \text{ mg.m}^{-3}$ . No information on relevant medical histories of the exposed individuals or on possible co-exposures to other irritant substances was provided. Nor is it clear whether the itching on the hands and face was due to dermal contamination as opposed to exposure to airborne peracetic acid. The fact that 8-hour TWA samples were taken means that nothing is known about any peak exposures to which staff might have been exposed. Because of the various limitations in the information provided in this report, no useful conclusions can be drawn concerning the hazards and associated exposure-response relationships for peracetic acid exposure.

The same authors also investigated the potential effects of inhalation exposure to peracetic acid on the teeth and gums on hospital personnel. The study group comprised 26 female hospital workers exposed to peracetic acid at measured concentrations of  $0.4 \text{ mg.m}^{-3}$  and above. These were matched to a control group of 26 women from a dental practice. Details were recorded of occupational and leisure activities to exclude damage to the teeth caused

by influences other than peracetic acid. The only observed difference between the two groups was a statistically significant increase in the sulcus bleeding index (indicative of gingivitis) in the area of the front teeth, in the peracetic acid-exposed group. No information was provided regarding the severity of effect, or whether assessments were conducted by investigators blinded to exposure status. Overall, the results point to the possibility of an increased risk of gingivitis in peracetic-acid exposed workers but given that no changes in dental enamel or other oral parameters were observed, no firm conclusions can be drawn from this report.

Three other reports were briefly cited in the ECETOC review (Ancker and Zetterberg, 1997 Dworschak and Linde, 1976, Tichacek, 1966). HSE has not pursued the original reports, as it seems from the ECETOC review that these are unlikely to provide anything useful.

### **Summary of exposure-response data for inhalation exposure to peracetic acid**

The reactive nature of peracetic acid means that local sensory irritant and inflammatory/corrosive effects in tissues at the immediate site of contact are of most concern for occupational health.

Single exposure studies in rats to aerosols of peracetic acid showed that after 25 minutes exposure to  $220 \text{ mg.m}^{-3}$  there was widespread necrosis of the nasal turbinates. The 4-hour  $\text{LC}_{50}$  value in rats is reported to be about  $200 \text{ mg.m}^{-3}$  (0.2 mg/l). These findings demonstrate that peracetic acid is very toxic on single inhalation exposure, and the upper respiratory tract is the key site of toxicity. No evidence for histopathological changes in the respiratory tract was seen following 25 minutes exposure of rats to  $35 \text{ mg.m}^{-3}$ .

In relation to human data concerning the effects of single inhalation exposure, no reliable quantitative information is available.

In relation to the effects of repeated inhalation exposure, no reliable information is available, either from human or animal data.

### **References**

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), (1993). Peracetic acid (Cas No 79-21-0) and its equilibrium solutions. Joint Assessment of Commodity Chemicals (JACC) No 40. ECETOC, Brussels, Belgium.

Gagnaire F, Marignac B, Hecht G and Hery M, (2002). Sensory irritation of acetic acid, hydrogen peroxide, peroxyacetic acid and their mixture in mice. *Ann occup hyg*, **46** (1), 97-102.

Harvey AJ (1992) Atmospheric test on Cidox formulation. Personal communication. Solvay Interlox, Warrington, Cheshire, UK.

Mc Donagh J (1997) Atmospheric monitoring of peracetic acid on the existing caprolactone plant distillation houses A and B, assessment of results. Personal communication. Solvay Interlox, Warrington, Cheshire, UK.

Simms RA (1995) Peroxygen atmospheric monitoring, Glan Clwyd Hospital Bodelyyddan. Personal communication. Solvay Interlox Warrington, Cheshire, UK.

## ANNEX 2

**PERACETIC ACID**

## IDENTITY AND PROPERTIES

CAS No:	000079-21-0
EEC No:	201-186-8
Formula	CH <sub>3</sub> COOOH
Synonyms	peroxyethanoic acid, peroxyacetic acid, ethaneperoxic acid, acetic peroxide, acetyl hydroperoxide

Partial vapour pressure 2.7 mBar for 35% peracetic acid

Boiling point 105 °C for 40% peracetic acid

## OCCURRENCE AND USE

Peracetic acid is a liquid with an acrid odour. In commercial formulations, peracetic acid is always in dynamic chemical equilibrium with acetic acid, hydrogen peroxide and water and dilution may result in changed equilibria. It is soluble in water, ethanol, ether, and sulphuric acid. Dilute solutions are stable.

Peracetic acid is used as a bactericide and fungicide, particularly in food and drinks processing. It can also be used as a reagent in chemical synthesis, as a bleaching and sterilising agent, as a polymerisation catalyst for polyester resins and as an oxidant for preparing epoxy compounds.

Growth is anticipated in usage as a slime control agent in the pulp/paper industry and as a replacement for glutaraldehyde in the sterilisation of medical devices in the health care industry.

## TOXICOKINETICS

There are no useful studies concerning the toxicokinetics of peracetic acid<sup>1</sup>. It is predicted that on inhalation exposure to peracetic acid vapour and/or aerosols, it will be deposited along the entire respiratory tract. Its reactive nature suggests that upon contact with respiratory tract or gastrointestinal tract epithelium it will be rapidly hydrolysed to acetic acid and hydrogen peroxide. No significant dermal absorption of unchanged peracetic acid through intact skin is anticipated although concentrated solutions will damage the skin and thereby enhance penetration.

HEALTH EFFECTS<sup>1</sup>

## Animal studies

Studies in rats indicate that peracetic acid is very toxic following single inhalation exposure to peracetic acid aerosols, with 4-hour LC<sub>50</sub> values of approximately 0.2 mg/l. Peracetic

acid is also very toxic following single oral exposure; the calculated LD<sub>50</sub> values obtained from different studies range from 7-300 mg/kg. Studies in rabbits indicate that peracetic acid is toxic following single dermal exposure, with LD<sub>50</sub> values of 50-65 and 230 mg/kg for two different strength solutions. For all routes of exposure, mortality responses are due to severe local effects at the site of contact.

Animal evidence indicates that aerosolised peracetic acid is a respiratory tract irritant, producing damage to the upper respiratory tract and marked decreases in respiratory rate in Alarie assays<sup>2</sup>. The RD<sub>50</sub> values observed were 12-23 mg.m<sup>-3</sup>. In acute inhalation studies no histopathological evidence of respiratory tract damage was observed following exposures to peracetic acid aerosols at measured concentrations of up to 36 mg.m<sup>-3</sup> for 25 minutes. Similar exposures at concentrations of 220 mg.m<sup>-3</sup> and above were found to cause widespread necrosis of the nasal turbinates and focal necrosis of the nasal vestibulum.

In relation to topical effects, solutions containing peracetic acid at concentrations of 5% and above were found to be corrosive to the skin of rabbits. No skin irritancy was observed following dermal application of a solution containing 0.034% peracetic acid for 24 hours. In this study, severe skin reactions were observed at concentrations of 0.34% and above. A 0.034% solution was not irritating to the rabbit eye but concentrations of 0.34% and above caused severe eye irritation.

No data are available on the skin irritation potential of peracetic acid in aerosol or vapour form. There is a brief report of severe eye effects following inhalation exposure to unstated concentrations of aerosolised peracetic acid. Given the corrosive properties of liquid peracetic acid, it is concluded that peracetic acid aerosol or vapour is likely to be corrosive to the skin and eyes. However, no exposure-response data for such effects are available.

No studies regarding the respiratory sensitisation potential of peracetic acid are available. Consideration of the chemical structure suggests a lack of protein-binding potential, and its breakdown products, hydrogen peroxide and acetic acid are not sensitisers. In relation to skin sensitisation, peracetic acid gave negative results in two modern Buehler studies. A negative result was also obtained in a maximisation test although this did not meet current standards for the conduct of such studies. Overall, it can be concluded that peracetic acid is unlikely to possess allergenic potential.

There are no useful/reliable studies of the effects of repeated inhalation exposure to peracetic acid in animals. The repeated-dose oral toxicity of peracetic acid has not been fully investigated, but the key effect is local damage to the gastrointestinal tract. Peracetic acid was found to cause severe local effects following repeated dermal application.

In relation to mutagenicity, a mixed pattern of results has been obtained in bacterial mutagenicity tests. However, where specific investigations were conducted with bacterial strains sensitive to the mutagenic effects of reactive oxygen species, negative results were reported. Peracetic acid tested negative for UDS *in vitro* in human fetal fibroblast cells. A positive result was obtained in a chromosomal aberration test using human lymphocytes, although only in the presence of marked cytotoxicity. It is possible therefore that the chromosomal damage observed was an indirect consequence of cytotoxicity rather than a direct genotoxic effect of peracetic acid. The overall pattern of results from *in vitro* tests suggests that peracetic acid is unlikely to be a direct acting genotoxicant. *In vivo*, no evidence of genotoxic potential was observed in mouse bone marrow micronucleus and liver UDS tests, all conducted to modern protocols. However, the reassurance provided by

these negative *in vivo* results is limited because adequate peracetic acid exposure of the internal tissues sampled in these tests was not demonstrated. Whether or not peracetic acid could be mutagenic in tissues at the site of contact has not been investigated, but it seems unlikely at non-cytotoxic concentrations.

Peracetic acid has not been thoroughly tested for carcinogenic potential. The only data relate to dermal exposure, indicating that peracetic acid caused an increased incidence of skin tumors. However, such tumors are likely to be due to chronic inflammation at the site-of-contact and are of limited relevance regarding the carcinogenic potential of peracetic acid solutions in occupational settings, at concentrations that do not cause persistent tissue inflammation. Overall, there are no strong clear indicators of carcinogenic potential of relevance to contemporary occupational conditions but the carcinogenic potential of peracetic acid has not been fully explored.

Very little information is available concerning the reproductive toxicity potential of peracetic acid. A briefly reported study identified no adverse effects on fertility following 10 month administration of 0.02% peracetic acid to rats in drinking water. No reliable studies are available to address the developmental toxicity of peracetic acid. However, as peracetic acid is rapidly hydrolysed on contact with biological tissues, distribution to the reproductive organs is not anticipated. Therefore, peracetic acid is unlikely to be a reproductive toxicant

#### Human Data

The only human data available relate to skin and respiratory tract irritation. Peracetic acid was found to be a skin irritant in a number of brief reports. Although sensory irritation has been reported in workers exposed to peracetic acid, no reliable quantitative data concerning exposure-response relationships are available. There are no documented cases of occupational asthma in workers exposed to peracetic acid, but it is predicted not to have sensitising properties.

#### REFERENCES

1 ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), (2001). Peracetic acid (Cas No 79-21-0) and its equilibrium solutions. Joint Assessment of Commodity Chemicals (JACC) No 40. ECETOC, Brussels, Belgium.

2 Gagnaire F, Marignac B, Hecht G and Hery M, (2002). Sensory irritation of acetic acid, hydrogen peroxide, peroxyacetic acid and their mixture in mice. *Ann Occup Hyg* **46**, 97-102

