8.5.2 Primary DNA-damage

Primary DNA-damage in bacteria (Table 40)

H_2O_2 induced DNA-repair in *Escherichia coli* (Thielmann and Gersbach, 1978; De Flora *et al*, 1984), SOS responses in *Salmonella typhimurium* (Nakamura *et al*, 1987) and *E. coli* (Von der Hude *et al*, 1988; Zhou *et al*, 1991). In the presence of metabolic activation, catalase or SOD, no effect was observed in the DNA-repair test or the SOS chromotest using *E. coli* strains (De Flora *et al*, 1984; Zhou *et al*, 1991).

DNA-strand breaks in cultured mammalian cells (Table 41)

H_2O_2 induced DNA single-strand breaks in bovine lens epithelial cells (Kleiman *et al*, 1990), rat intestinal epithelial cells (Grisham and Kvietys, 1989), L1210 leukemia cells (Hincks and Gibson, 1988/89), rat hepatocytes (Olson, 1988), L5178 Y mouse lymphoma cells (Garberg *et al*, 1988), P388D1 cells (Schraufstatter *et al*, 1986), rat and human lymphocytes (Schraufstatter *et al*, 1986; Grisham and Kvietys, 1989), human bronchial epithelial cells (Saladino *et al*, 1985), JB6 Cl 21 cells (Gensler and Bowden, 1983) or V79 cells (Bradley *et al*, 1979; Bradley and Erickson, 1981; Prise *et al*, 1989).

DNA double-strand break induction was observed in V79 cells (Prise *et al*, 1989) and in human leucocytes (Cristovão *et al*, 1991) but not in cultured rat hepatocytes (Olson, 1988). Decreased DNA and RNA synthesis in human bronchial cells was observed (Saladino *et al*, 1985) after treatment with H_2O_2, but there was no or a relatively insignificant induction of DNA-protein (Bradley *et al*, 1979; Bradley and Erickson, 1981; Olson, 1988; Kleiman *et al*, 1990) or DNA-DNA crosslinks (Bradley *et al*, 1979; Bradley and Erickson, 1981).

Unscheduled DNA Synthesis (UDS) in cultured mammalian cells (Table 42)

Unscheduled DNA Synthesis was observed in rat hepatocytes (Cattley *et al*, 1988; Beales and Suter, 1989) and human cells (Stich *et al*, 1978; Coppinger *et al*, 1983) after *in vitro* treatment with H_2O_2.

Sister Chromatid Exchanges (SCE) in cultured mammalian cells (Table 43)

H_2O_2 induced Sister Chromatid Exchanges (SCE) in V79 cells (Bradley *et al*, 1979; Speit *et al*, 1982; Mehnert *et al*, 1984a,b; Speit, 1986; Tachon and Giacomoni, 1989), CHO cells (Mehnert *et al*, 1984a,b; Tucker *et al*, 1989; Wilmer and Natarajan, 1981), human D98/AH2 cells (Estervig and Wang, 1984) and human lymphocytes (Mehnert *et al*, 1984a,b). In the presence of S9, catalase or peroxidase, SCE-induction was reduced or inhibited (MacRae and Stich, 1979; Speit *et al*, 1982; Mehnert *et al*, 1984a,b).

TABLE 40

PRIMARY DNA-DAMAGE IN BACTERIA

Test system	Metabolic activation	Concentration (μM)	Results (lowest positive response)	Reference
SOS chromotest				
E. coli PQ37	No	0-500	+ve (20μM)	Zhou *et al*, 1991
	Catalase	20	-ve	
	SOD	20	-ve	
SOS chromotest				
E. coli PQ37	No	0-1,000	+ve (0.3mM)	Von der Hude *et al*, 1988
Umu test				
Salmonella typhimurium TA1535/pSK1002	No	Unknown	+ve (45mg/ml)	Nakamura *et al*, 1987
DNA-repair test				
E. coli WP2, WP67 and CM871	No	Unknown	Minimal inhibitory concentration was 0.02μg	De Flora *et al*, 1984
	S9	Unknown	-ve	
DNA excision repair				
E. coli	No	0-400,000	+ve	Thielmann and Gersbach, 1978

TABLE 41

PRIMARY DNA-DAMAGE IN CULTURED MAMMALIAN CELLS - INDUCTION OF DNA-STRAND BREAKS

Test system	Metabolic activation	Treatment time/ temperature	Concentration (μM)	Results (lowest effective concentration)	Reference
Human leucocytes	No	10min/ Unknown	500-1,000	Dose-dependent induction of DNA double strand breaks	Cristovao *et al*, 1991
Bovine lens epithelial cells	No	5min/37°C	10-200	Linear increase of DNA single-strand breaks (50μM)	Kleiman *et al*, 1990
Rat intestinal epithelial cells	No	15min/37°C	100	Induction of DNA-strand breaks	Grisham and Kvietys, 1989
Lymphocytes	No	15min/37°C	100	Induction of DNA-strand breaks	Grisham and Kvietys, 1989
V79 cells	No	10-20min/0°C	10-1,000	Dose-dependent induction of DNA single-strand breaks (10μM)	Prise *et al*, 1989
V79 cells	No	20min/0°C	10-10,000	Induction of DNA double-strand breaks at concentration higher than 100μM	Prise *et al*, 1989
L1210 leukemia cells	No	1h/0°C	50-200	Dose-dependent formation of DNA strand breaks (50μM)	Hincks and Gibson, 1988/89
Rat hepatocytes	No	1h/37°C	10-1,000	Concentration-dependent increases in single-strand DNA breaks (10-50μM) but lack of induction of double-strand DNA breaks	Olson, 1988
Rat hepatocytes	No	1h/37°C	200/500	Lack of H_2O_2-induced DNA-protein cross linking	Olson, 1988

TABLE 41 (cntd.)

RIMARY DNA-DAMAGE IN CULTURED MAMMALIAN CELLS - INDUCTION OF DNA-STRAND BREAKS

Test system	Metabolic activation	Treatment time /temperature	Concent-ration (μM)	Results (lowest effective concentration)	Reference
L5178Y Mouse Lymphoma cells	No	3h/37°C	2,000-2,510	Concentration-related increase in single-strand DNA breaks (2000μM)	Garberg *et al*, 1988
P388D1 cells and human lymphocytes	No	5min/37°C	25-1,000	Concentration-related increase in single-strand DNA breaks (25μM)	Schraufstat-ter *et al*, 1986
Normal Human Bronchial Epithelial Cells	No	1h/37°C	100 or 120	Decrease DNA and RNA synthesis Induced DNA single-strand breaks	Saladino *et al*, 1985
JB6Cl21 cells	No	1h/37°C	1-100	Concentration-dependent increase in single-strand breaks (10μM)	Gensler and Bowden, 1983
V79 cells	No	2h/1°C	7.4-73.5	Concentration-dependent increase in single-strand breaks(14.7μM)	Bradley and Erickson, 1981
	No	1h/1°C	353	No induction of DNA-protein or DNA-DNA crosslinks	Bradley and Erickson, 1981
V79-4 cells	No	Unknown	353	Induction of DNA single-strand breaks and/or alkali-labile lesions No induction of DNA-protein or DNA-DNA crosslinks	Bradley *et al*, 1979

TABLE 42

PRIMARY DNA-DAMAGE IN CULTURED MAMMALIAN CELLS - INDUCTION OF UNSCHEDULED DNA SYNTHESIS (UDS)

Test system	Protocol	Exposure time (h)	Metabolic activation	Concent-ration (mM)	Results (lowest effective concentration)	Reference
Rat hepatocytes	Liquid scintillation	20	No	0.1-100	Concentration related increase (1mM)	Beales and Suter, 1989
Rat hepatocytes	Auto-radiography	3x1	No	1.9-6.4	Induction of UDS (3.2mM)	Cattley *et al*, 1988
WI-38 CCL75 cells (human diploid fetal lung cells)	Auto-radiography	3-4	No	0.6-2400 µg/ml	Concentration-related increase (9µg/ml)	Coppinger *et al*, 1983
	Differential density labeling	3-4	No	0.15-600 µg/ml	Concentration-related increase (9.4µg/ml)	Coppinger *et al*, 1983
Human fibroblastes	Auto-radiography	3	No	0.1-10	Concentration-related increase (0.6mM)	Stich *et al*, 1978

TABLE 43 - PRIMARY DNA-DAMAGE IN MAMMALIAN CELLS - INDUCTION OF SISTER CHROMATID EXCHANGES (SCE)

Test system	Metabolic activation	Exposure time (h)	Concentration (μM)	Cyto-toxicity (IC_{50}) (μM)	Results (lowest effective concentration)	Reference
V79 cells	No	1	5-20	>20 in MEM 5-10 in PBS	No SCE induction in MEM culture medium Concentration related induction of SCE (10μM) in PBS medium	Tachon and Giacomoni, 1989
CHO cells	No	15-22	40-240	160	Induction of highly significant levels of SCE and endoreduplicated cells (40μM and 160μM, respectively)	Tucker *et al*, 1989
V79 cells	No	3	10-80	20-40	Induction of SCE (20μM)	Speit, 1986
Whole human blood or human purified lymphocytes	No	24	20-2,000	Unknown	SCE induction in purified lymphocytes (20μM) but not in whole blood culture	Mehnert *et al*, 1984a
	No	2	80-200	Unknown	SCE induction in purified lymphocytes (80μM) but not in whole blood culture	Mehnert *et al*, 1984a
Human purified lymphocytes	Catalase or peroxydase or S9-mix	2	80-200	Unknown	Reduction of H_2O_2-induced SCEs	Mehnert *et al*, 1984a
D98/AH2 human cells	No	24	15-60	>60	3-fold SCE induction at 60μM	Estervig and Wang, 1984
CHO cells	No	2	0.1-100mM	10mM	Slight increase of the SCE frequency (0.5mM)	Wilmer and Natarajan, 1981

TABLE 43 (Cntd)

Test system	Metabolic activation	Exposure time (h)	Concentration (μM)	Cyto-toxicity (IC_{50}) (μM)	Results (lowest effective concentration)	Reference
CHO cells	No	24	0.3-7.8	No toxicity	Two-fold increase of SCE (3.9μm)	MacRae and Stich, 1979
	Catalase	Un-known	5-100	No toxicity	Complete reduction of the H_2O_2-induced SCE	MacRae and Stich, 1979
V79 and CHO cells	No	1 or 24	10-40	Un-known	Concentration-related induction of SCE (10-20μM)	Mehnert *et al*, 1984b
	S9-mix	1	10-40	Un-known	Inhibition of SCE-induction	Mehnert *et al*, 1984b
V79 cells	No	1 or 9	1-800	Un-known	Induction of SCE	Speit *et al*, 1982
	Catalase	9	100-800	Un-known	Complete reduction of the H_2O_2-induced SCE	Speit *et al*, 1982
CHO cells	No	2	100-100,000	>10,000 μM	Slight increase of the SCE frenquency (500μM)	Wilmer and Natarajan, 1981
V79 cells	No	Un-known	353	20% survival	Two-fold increase of the SCE frequency	Bradley *et al*, 1979
CHO cells	No	24	0.31-7.8	No toxicity	Two-fold increase of the SCE frequency (3.9μM)	McRae and Stich, 1979
	Catalase	Un-known	5-100	No toxicity	Complete reductions of the hydrogen peroxide induced SCE's	McRae and Stich, 1979

8.5.3 Clastogenicity

Chromosomal aberrations in cultured mammalian cells (Table 44)

Chromosome aberrations (mainly chromatid breaks or micronuclei) were induced in V79 cells (Tsuda, 1981; Tachon and Giacomoni, 1989), Don-6 Chinese hamster cells (Sasaki *et al*, 1980), human embryonic fibroblasts (Oya *et al*, 1986), human leucocytes (Cristovão *et al*, 1991), CHO cells (Stich *et al*, 1978; Tsuda, 1981; Stich and Dunn, 1986), CHL cells (Ishidate *et al*, 1984), Syrian hamster and Balb/c mouse cells (Tsuda, 1981), but not in D98/AH2 human cells (Estervig and Wang, 1984) after *in vitro* treatment with H_2O_2.

In vitro exposure of murine splenocytes to H_2O_2 did not increase the frequency of micronucleated cells (Dreosti *et al*, 1990). This negative result may be due to the use of the culture medium as the solvent for H_2O_2 and inadequate H_2O_2 concentrations (Oya *et al*, 1986). Combined treatment with ferrous ions and H_2O_2, led to a synergistic enhancement of the frequency of micronuclei (Dreosti *et al*, 1990).

Chromosomal aberrations and micronuclei induction in mammals

Forty-eight hours after implantation of ascite-tumours (S2 sarcoma, Ehrlich ascites carcinoma and sarcoma 180), mice were injected i.p. with 0.2ml H_2O_2 solution at concentrations ranging from 0.01 to 0.5M; 48h later, the treated and untreated tumours were examined. A dose-related increase in the number of chromosomal aberrations of the tumour cells was observed in the H_2O_2 treated mice (Schoeneich, 1967).

H_2O_2 did not induce chromosomal aberrations in bone-marrow cells of rats (Kawachi *et al*, 1980) and was negative in a micronucleus test in mice (Keck *et al*, 1980). Details of these two studies are lacking.

8.5.4 Genotoxicity in Cultured Mammalian Cells - Other End-points

H_2O_2 caused morphological transformation of C3H/10T1/2 cells (Nassi-calo *et al*, 1989).

8.5.5 Mechanistic Considerations

According to several authors, DNA appears to be the main cellular target of H_2O_2, but its cytotoxicity limits the expression of its genotoxic potential *in vitro* (Sanford *et al*, 1986; Meneghini, 1988; Cantoni *et al*, 1989; Ruch *et al*, 1989).

The formation of adenine N-1-oxide (Mouret *et al*, 1990), 8-hydroxyguanosine (Kasai *et al*, 1986), thymidine glycol (Frenkel and Chrzan, 1987), H_2O_2-induced alkali-labile sites (including

TABLE 44

CHROMOSOMAL ABERRATIONS IN CULTURED MAMMALIAN CELLS

Test system	End-point	Exposure time (h)	Metabolic activation	Concentration (μM)	Results (lowest effective concentration)	Reference
Human leucocytes	Chromosomal aberrations	24	No	15 and 20mM	Six-fold increase at 20mM	Cristavao *et al*, 1991
Murine splenocytes	Cytokinesis-block micronucleus assay	Unknown	No	10 and 20	No increase of the frequency of micronucleated splenocytes	Dreosti *et al*, 1990
		Unknown	Ferrous ions	20	Synergistic enhancement in micronucleus frequency	Dreosti *et al*, 1990
V79 cells	Micronuclei	1	No	10-20	Concentration-related increase of micronuclei (10μM) in PBS* medium, no effect in MEM* medium	Tachon and Giacomoni, 1989
Human embryonic fibroblasts	Chromosomal aberrations Chromatid aberrations	10 min	No	10-1,000	Concentration-related increase of chromosomal and chromatid aberrations (20μM)	Oya *et al*, 1986
CHO cells	Chromosomal aberrations and micronuclei	3	No	<10-25	Concentration-related increase of chromosome aberrations (12.5μM), chromatid translocations (12.5μM) and micronuclei (12.5μM)	Stich and Dunn, 1986
CHL cells	Chromosomal aberrations	24/48	No	0-7.3	Positive at 24h (3.7μM) and 48h (1.8μM)	Ishidate *et al*, 1984

* PBS, Phosphate-buffered saline; MEM, Eagles Modified Minimal Essential Medium.

TABLE 44 (cntd)

CHROMOSOMAL ABERRATIONS IN CULTURED MAMMALIAN CELLS

Test system	End-point	Exposure time (h)	Metabolic activation	Concentration (μM)	Results (lowest effective concentration)	Reference
D98/AH_2 human cells	Chromosomal aberrations	24	No	15-60	Negative	Estervig and Wang, 1984
CHO-K1 cells	Chromosomal aberrations	3	No	100-1,000	Concentration-related increase of chromatid breaks (200μM)	Tsuda, 1981
V79 cells	Chromosomal aberrations	3	No	100-1,000	Concentration-related increase of chromatid breaks (200μM)	Tsuda, 1981
Syrian hamster cells	Chromosomal aberrations	3	No	100-1,000	Concentration-related increase of chromatid breaks (200μM)	Tsuda, 1981
Balb/c mouse cells	Chromosomal aberrations	3	No	10-100	Concentration-related increase of chromatid breaks (50μM)	Tsuda, 1981
CHO cells	Chromosomal aberrations	2	No	100-100,000	Only positive at 10,000μM	Wilmer and Natarajan, 1981
CHO cells	Chromosomal aberrations	3	No	100-1,000	Concentration related increase of chromosome aberrations (100μM), toxic at concentrations higher than 300μM	Stich *et al*, 1978
Don-6 cells (Chinese hamster cells)	Chromosomal aberrations	3	No	500-2,000	Dose related increase of chromosome aberrations (1,000μM)	Sasaki and Sugimura, 1980

DNA strand-breaks), SCEs, gene mutations, chromosomal aberrations, DNA-repair and cell transformations are all mediated by hydroxyl radicals (·OH) aimed at the DNA by DNA-bound transition metals (Emerit *et al*, 1982; Oya *et al*, 1986; Joenje, 1989; Tachon, 1990). These effects can be inhibited by the addition of a strong Fe-chelating agent or a hydroxyl radical (·OH) scavenger (Mello Filho and Meneghini, 1984; Oya *et al*, 1986; Cantoni *et al*, 1989; Nassi-Calo *et al*, 1989) and enzymes that catalytically scavenge intermediates of oxygen reduction ($O_2^{\cdot-}$ and H_2O_2) (section 7).

No specific defences are known against ·OH radicals and singlet oxygen which react quickly with almost any biologically active molecule.

The *in vivo* data show discrepancies between positive results observed in host-mediated assays (gene mutations and chromosomal aberrations) and negative results in chromosomal aberration tests in rats and micronucleus tests in mice. Several reports confirm that sensitivity to exogenous H_2O_2 is negatively correlated with cellular catalase activity in mammalian cells (Winquist *et al*, 1984; Vuillaume, 1987; Sawada *et al*, 1988). The low catalase activity of tumour cells used in the host mediated assay (Schoeneich, 1967) and the direct contact with H_2O_2 by i.p. administration may explain the positive results in the host-mediated assays. On the other hand, the absence of chromosomal abnormalities in the bone-marrow of the orally treated animals may be explained by decomposition of H_2O_2 in the bowel before absorption and by the high catalase activity of red blood cells, which can decompose H_2O_2 after its absorption.

8.5.6 Evaluation

The *in vitro* and *in vivo* genotoxic potential of H_2O_2 is summarised in Table 45.

In conclusion, since only hydroxyl radicals and singlet oxygen are capable of damaging DNA directly, the genotoxic potential of H_2O_2 depends on the accessibility of the extremely reactive hydroxyl radical to its target DNA. *In vitro*, the bacteria or other cells come into direct contact with H_2O_2 and genotoxic effects can be induced; in general, the addition of an exogenous metabolic agent or catalase reduces or abolishes the mutagenic response. *in vivo*, many factors contribute to the reduction of the bioavailability of H_2O_2 for systemic genotoxic action. However, the occurrence of genotoxic effects on cells which are in direct contact with H_2O_2 (at the site of application) cannot be excluded.

TABLE 45

EVALUATION OF GENOXICITY

End-Point	Test System	Results
IN VITRO		
Gene mutation	*Salmonella typhimurium*	+ve without activation decrease of the genotoxic potential in presence of exogenous S9 or catalase
	Escherichia coli	+ve without activation
	Saccharomyces cerevisiae	+/-ve without activation
	Bacillus subtilis	+ve without activation
	Mammalian cells	+ve without activation
Primary DNA-damage		
DNA-repair	*Salmonella typhimurium*	+ve without activation
	Escherichia coli	+ve without activation -ve with activation
DNA-strand break SCE	Mammalian cells	+ve without activation
	Mammalian cells	+ve without activation
	Mammalian cells	+ve without activation decrease of the SCE induction in presence of exogenous S9 or catalase
Chromosomal aberration	Mammalian cells	+ve without activation
Morphological transformation	Mammalian cells	+ve without activation
IN VIVO		
Gene mutation	Drosophila melanogaster	-ve
	Salmonella typhimurium (host mediated assay in mice)	+ve
Chromosomal aberration		
Micronucleus Metaphase analysis	Mice	-ve
	Rat	-ve
	Tumour cells (host mediated assay in mice)	+ve

8.6 REPRODUCTIVE TOXICITY/TERATOGENICITY

8.6.1 Male Fertility

The spermicidal activity of H_2O_2 was investigated both *in vivo* and *in vitro*. Washed and unwashed sperm from bull, rabbit, ram, fowl, dog and mouse were exposed to solutions containing .3, 3, 30, 300 and 3,000ppm H_2O_2. Sperm were evaluated for mobility *in vitro* following washing and when added directly to diluent. There were large species differences in the tolerance to H_2O_2. Rabbit spermatozoa were the most resistant and bull and fowl were the least resistant to the immobilising effect of H_2O_2. Although 3ppm had small, but significant effects on bull and fowl spermatozoa, concentrations 10 to 100 times greater were required to immobilise rabbit spermatozoa. In general, washing increased the toxicity of H_2O_2, but this effect varied with the species tested. Bull and fowl spermatozoa were least affected by washing and rabbit spermatozoa were most affected (Wales *et al*, 1959). Endogenous catalase is removed when spermatozoa are washed; thus, washing the spermatozoa is expected to increase the toxicity of H_2O_2.

Male albino mice were given 0.33%, 1.0% or 3.0% H_2O_2 solutions in place of drinking water. There were no controls. The mice at the highest dose (3.0%) would not drink the solution and were taken off the study. Mice were mated after 7 and 21d on H_2O_2. All females became pregnant within a few days and delivered litters of normal size. The concentration, morphology and mobility of the spermatozoa of the male mice and rabbits receiving H_2O_2 in their drinking water over 3 and 6 weeks remained normal. *In vivo*, H_2O_2 has no significant spermicidal action in mice at concentrations up to 1% in solution (Wales *et al*, 1959).

8.6.2 *In Vitro* Embryotoxicity

The embryotoxicity of 30% H_2O_2 was investigated using 3-day old (72-76h) Leghorn chicken eggs (Korhonen *et al*, 1984). H_2O_2 solutions (0.05, 0.09, 0.19 and 0.37mg/egg) were dropped on the inner shell membrane in the egg's air chamber, focussing on the embryo visible under the membrane. The ED_{50} for all effects observed was 0.9mg/egg. The LD_{50} was 1.2mg/egg. The NOEL was 0.05mg/egg based on embryo-lethality and toxicity. The significance of this type of study to mammalian species is uncertain.

8.6.3 Reproductive Organs

Male and female rats were administered H_2O_2 by gavage at doses of 1/10-1/5 LD_{50}. Several effects were reported: modification of the oestrus cycle in females and a decrease in sperm mobility in males. Male and female rats received daily doses of 0.005-50mg/kg H_2O_2 by gavage for 6 months. At the high dose, females showed modifications of the oestrus cycle and males reduced mobility of spermatozoa. Treated animals were mated. Among high dose

females, only 3/9 produced litters, compared to 7/9 in the control group. In addition, the body weight of the offspring of the high dose females was reduced relative to those of control females (Antonova, 1974).

8.6.4 Teratology

An attempt was made to assess the teratogenic potential of H_2O_2 in the rat. H_2O_2 was mixed with powdered feed to give 0.02, 0.1, 2 and 10% in the diet which was fed to female rats for 1 week during their 'critical period' of gestation. Unfortunately, this study has multiple deficiencies including a poor design which led to severe reduction of food intake, lack of diet analysis and too few animals for a meaningful statistical analysis. The authors acknowledged that H_2O_2 decomposes readily and showed that the level in the 2% diet declined to background level within 3d. Thus no conclusion regarding the teratogenic potential of H_2O_2 can be made from this study. (Moriyama *et al*, 1982).

A brief communication published over 30 years ago described a study in which 3 rat dams were given 0.45% H_2O_2 to drink. After 5 months, the H_2O_2 was replaced with water and they were mated; all 3 produced normal litters (Hankin, 1958). However, no details regarding study design or conduct were given, thus precluding any evaluation of the adequacy of this study.

8.6.5 Evaluation

Data on the teratogenic potential and reproductive toxicity are too limited to allow an evaluation.

SECTION 9. EFFECTS ON MAN

9.1 ACCIDENTAL EXPOSURE INCIDENCE (TABLE 46)

Reports of accidental exposure resulting in treatment at poison control centres have been tabulated by the American Association of Poison Control Centers since 1985 (Litovitz *et al*, 1990). Similar data on the European situation are not available. In 1989, there were 7,354 cases of accidental exposure due to consumer use of H_2O_2 as a household topical disinfectant (4,293 cases in 1987). There were 8,557 additional cases due to contact with cosmetic/personal care products containing peroxide (7,587 cases in 1987). The combined number in 1989 (15,911) was greater than the total number of cases reported in 1987 (11,871) (Litovitz *et al*, 1988).

TABLE 46

ACCIDENTAL EXPOSURES IN THE USA IN 1989

(Litovitz *et al*, 1990)

Total number of exposures	Age Group (y)			Reason		Treated in Health Care Facility
	<6	6-17	>17	Accident	Intention	
Topical use						
7,354[a]	4,613	590	2,100	7,199	138	487
Cosmetic and personal care use						
8,557[b]	5,073	669	2,717	8,291	229	727

a Outcomes of exposure included 2,071 cases with no toxicity, 1,395 cases of minor toxicity and 37 cases of moderate toxicity. There were no deaths.

b Outcomes of exposure included 2,619 cases with no toxicity, 1,917 cases of minor toxicity, 75 cases of moderate toxicity and 3 cases of major toxicity. There were no deaths.

9.2 ACUTE ORAL TOXICITY

A 1-year-old child died of respiratory failure within one hour after ingesting an unknown quantity of a 30% H_2O_2 solution (Giusti, 1973). Post-mortem examination revealed extensive hypostasis and petechiae of the thymus, epicardium and duodenum. The stomach was distended with gas and the viscera were congested. There was some necrosis of the gastro-intestinal mucosa.

A 2-year-old boy ingested an unknown amount of a 3% H_2O_2 solution. He was foaming around the mouth and had vomited three times. A gas embolism was visualised in the portal venous system. It was concluded that liberation of oxygen from H_2O_2 in the stomach ascended through the gastric veins to the portal venous system. The child recovered (Rackoff and Merton, 1990).

A 26-month-old girl ingested a mouthful of a 35% H_2O_2 solution. The child vomited spontaneously. Clinical signs included lethargy and bright red-tinged, frothy emesis. She experienced one fainting episode with short cessation of respirations which returned spontaneously. Endoscopy 16h after exposure showed erosion of the cardiac stomach and erythema of the lower oesophageal sphincter and a gastric burn. Follow-up endoscopy 12d later showed normal esophageal and duodenal mucosa with minimal hyperemia of the cardiac stomach and no ulceration or eschar of the gastric mucosa. The child recovered completely within 2 weeks (Humberston *et al*, 1990).

A 3-year old girl died following ingestion of an unknown quantity of 40% H_2O_2 solution. Pathological findings at autopsy included oedema of the lungs and small erosions of the stomach mucosa, probably due to the lavage tube used to wash out the stomach. The report indicates that the probable cause of death was asphyxia due to obstruction of the distal respiratory tract by the foam liberated by the peroxide (oxygen gas) (Zecevic and Gsparec, 1979).

A 6-year old girl died and her four-year old friend was in critical condition with oropharyngeal burns after accidentally ingesting a solution of 35% H_2O_2 (Thompson, 1989).

Five non-fatal poisonings in adults were reported following consumption of about 25-100ml of H_2O_2 (concentration unknown). The victims experienced sharp pains in the abdomen, foaming at the mouth, vomiting, transitory loss of consciousness, sensory and motor impairment and elevated temperature. Microhaemorrhages of the skin and conjunctiva and moderate leukocytosis were also reported. One person exhibited marked visual (including temporary blindness) and neurological symptoms after swallowing 100ml of the H_2O_2 solution. Symptoms were considered to be due to microemboli of generated oxygen. All victims recovered completely in two to three weeks (Budagovskij *et al*, 1971).

A near-fatality occurred when a 33 year-old woman unintentionally ingested the contents of a 1 pint bottle (<500ml) of 35% H_2O_2. The patient was cyanotic and experienced seizures and foaming at the mouth. The abdomen was slightly distended. Neurological signs included lack of spontaneous eye movement, no verbal response and withdrawal from noxious stimuli. Laparotomy revealed air bubbles in the stomach but no perforations. Recovery was complete following treatment (Giberson *et al*, 1989).

9.2.1 Evaluation

Young children are particularly vulnerable to accidental ingestion of H_2O_2. Deaths have been reported from ingestion of unknown quantities of H_2O_2 solutions of 30-40% concentration.

9.3 INTENTIONAL EXPOSURE: MISUSE

There are a number of unofficial reports that some individuals self-administer H_2O_2 under the impression that it can provide health benefits. Such intentional exposure can lead to life-threatening toxicity, including death. A recent publication highlights the dangers of misuse of H_2O_2. A 39-year old man was admitted to a hospital emergency room in haemolytic crisis 24h after alleged intravenous injection of H_2O_2 (amount and concentration not specified), provided by a local physician, for treatment of cancer. Clinically, the patient was experiencing an acute haemolytic crisis (haematocrit 13.5%). He died following cardiopulmonary arrest on his twelfth day in the hospital (Jordan *et al*, 1991).

9.4 ACUTE EFFECTS FROM IRRIGATING AND CLEANSING SOLUTIONS

9.4.1 Oral Rinses

In a study designed to evaluate the antiseptic activity of a mouth rinse containing 0.5% or 0.75% H_2O_2 in 33% or 50% glycerine, respectively, no irritation of the oral mucosa was noted at the lower concentration in six subjects over a five-day use period with two one-minute rinses daily. Some subjects noted irritation of the mouth and gums at the higher concentration of H_2O_2, but these effects may have been due to the humectant effect of the 50% glycerine (Slanetz and Brown, 1949).

Rees and Orth (1986) report that the use of 3% H_2O_2 three to five times/day as a mouthrinse resulted in mucosal irritations in two individuals with prior tissue injury. The pre-existing lesions worsened after exposure to 3% solution. Herrin *et al.* (1987) has shown that use of 3% H_2O_2 with sodium bicarbonate did not cause any lesions in healthy individuals. Gingival lesions were seen in patients who used home care solutions employing 5M sodium chloride in addition to 3% H_2O_2 and sodium bicarbonate.

A group of 88 dental students self-administered 6-12.5% H_2O_2 solutions. They used it as a mouthwash and dipped their toothbrushes into the solution before brushing their teeth. Application of the H_2O_2 was 2-3 times/day for 1-2.5 months. Some gingival changes were noted: 6.4% of the subjects showed "redder" gums, 3.4% showed "paler" gums and 6.6% developed hyperkeratinised filiform papillae of the tongue (Miller *et al*, 1938).

The US FDA concluded that concentrations of up to 3% H_2O_2 are safe for over-the-counter use on the mucous membranes of the mouth and throat (US FDA, 1983).

9.4.2 Wound Irrigating and Disinfecting Solutions

A 3% solution of H_2O_2 is widely used as a topical antiseptic agent for suppurative wounds and inflammations of the skin and mucous membranes; as an irritating solution during root-canal therapy and as a mouth rinse for acute necrotising gingivitis (US FDA, 1983).

Cases of rupture of the colon, inflammation of the anus or rectum and ulcerative colitis have been reported following H_2O_2 use of a 1% or 2% solution as an enema (Pumphrey, 1951; Ludington *et al*, 1958; Sheehan and Brynjolfsson, 1960). This is no longer used.

Shock and coma developed suddenly in a 54-year old patient in which 3% H_2O_2 was being used for wound irrigation of the inguinal area during surgery. The patient recovered within one hour. The cause of the near-fatality was considered to be microembolisms formed by H_2O_2 degradation in the closed spaces of the wound irrigation (Bassan *et al*, 1982).

Oxygen embolism has been reported in several infants following intestinal irrigation with H_2O_2 to remove meconium (Danis *et al*, 1967; Shaw *et al*, 1967). In one case, a 36-h old infant died following use of 1% H_2O_2 to remove inspissated meconium from the bowel due to meconium ileus (Shaw *et al*, 1967).

There are several reports of chemically-induced colitis in patients undergoing endoscope examination with instruments which had been cleaned with 3% H_2O_2 (Jonas *et al*, 1988; Bilotta and Waye, 1989). Discrete white plaques adherent to the colonic mucosa and mild to severe erythema of the surrounding mucosa were observed in one report of twenty patients (Jonas *et al*, 1988). In the other reports, areas of white mucosa extending over areas of the colon were seen following endoscopic procedures (Bilotta and Waye, 1989). Pathological examination of biopsy specimens revealed nonspecific inflammation. Colitis has also been reported in patients following the use of 3% H_2O_2 diluted with water as an enema (Meyer *et al*, 1981).

Use of H_2O_2 to sanitise haemodialysis equipment has resulted in haemolysis in three pediatric patients, as shown by a significant decline in blood haemoglobin levels (Gordon *et al*, 1990). Apparently, the H_2O_2 sanitising solution was not adequately rinsed out prior to use.

A United States Food and Drug Administration panel indicated that 3% H_2O_2 is safe for over-the-counter use as a topical antiseptic and cleansing solution and sanitising lotions (US FDA, 1983).

9.5 OCULAR EXPOSURE

Several early reports indicate that H_2O_2 was used directly in human eyes to treat corneal ulcers, particularly in herpetic dendritic keratitis (Grant, 1986). In one case, a 20% solution was applied after a local anaesthetic every two hours, as a localised cautery to the ulcer. No apparent corneal damage resulted (Vala, 1965). A 10% solution of H_2O_2 was dropped on one eye of a patient after cocaine with no adverse consequences (Lewin and Guillery, 1913). It is not known how much reliance can be placed on these reports.

Historically, 1-3% solutions have been used as topical ocular antibacterial agents three to five times per day without significant injury (Grant, 1986). Dropping 3% H_2O_2 solution into human eyes causes severe pain, which soon subsides. Even a 0.5% solution caused pain and conjunctival hyperemia (Grant, 1986).

An accident report describes ocular inflammation, hyperaemia, tears and eyelid spasm in a woman who inadvertently placed in her eye a contact lens which had been stored in 3% H_2O_2. Vision was reduced insignificantly and recovery was complete in a few days following treatment with anti-inflammatory drops (Knopf, 1984).

Contact lens solutions of H_2O_2 generally contain buffers and preservatives which may reduce the ocular toxicity. The threshold irritant concentration was determined by introducing hydrogel contact lens treated with various concentrations of H_2O_2 into human eyes. Concentrations of 0, 25, 50, 100, 200, 400 and 800ppm were tested; none affected the physiological integrity of the eye. An initial conjunctival hyperemia occurred with the 800 and 400ppm levels by not with 200ppm and below. Levels of H_2O_2 in excess of 100ppm were associated with an initial subjective stinging response. Subjective effects, such as stinging were first noticed between 50 and 100ppm; the NOEL was 50ppm. There were no disruptive changes to the corneal or conjunctival epithelium at any concentration (Paugh *et al*, 1988).

The mean ocular threshold for discomfort in human subjects was 247ppm when solutions were instilled directly into the eyes (McNally, 1990).

H_2O_2 has gained wide-spread use as a disinfectant of contact lenses, resulting in maximum residual concentrations of 50-60ppm after neutralisation; this is close to the natural background level of H_2O_2 in the eye lens (section 7).

9.6 DERMAL EXPOSURE

A characteristic temporary whitening of the skin occurs after dermal application of 20% to 30% H_2O_2. The whitening is due to oxygen bubbles acting as microemboli in the capillaries and blocking circulation (Hauschild *et al*, 1958). H_2O_2 is used topically to bleach hair at concentrations of 3% to 6%. No clear data are available on the skin irritation effects of various H_2O_2 solutions in human beings (see also next section).

9.7 VAPOUR EXPOSURE

There are few reports of adverse effects resulting from inhalation exposure to H_2O_2, although bleaching of the hair is a common occurrence. Bleaching has been known to occur with levels of 0.5-1ppm vapour (FMC, 1990e), but it is uncertain whether bleaching was due to vapour exposure or to transfer of H_2O_2 from the hands to hair.

Eye and throat irritation and gradual bleaching of hair have been reported among factory workers exposed to H_2O_2 aerosol concentrations of 12 to 41mg/m^3 (8.6 to 29.5ppm) (Kaelin *et al*, 1988). The workers were operators of a semi-automatic milk packing machine which used a H_2O_2 bath to sanitise cardboard packaging for milk. One worker developed interstitial lung disease and impaired gas exchange, but since he was a heavy smoker, the cause of the pulmonary disease could not be ascertained.

In a USSR study, the irritant threshold to the lungs was determined in human volunteers exposed from 5 minutes to 1-4h. The threshold level was considered to be 10mg/m^3 for the full period (up to 4h) with a NOEL of 5mg/m^3 (Kondrashov, 1977). Increasing the time over which skin was exposed to H_2O_2 aerosols from 5min to 4h decreased the irritation threshold from 180 to 20mg/m^3 (Krondrashov, 1977).

9.8 INDIVIDUAL SUSCEPTIBILITY

Some individuals are more susceptible to H_2O_2 exposure because of hereditary disorders in H_2O_2 metabolising enzymes (section 7).

9.9 SKIN SENSITISATION

No data are available.

9.10 CHRONIC TOXICITY AND CARCINOGENICITY

No data are available.

9.11 REPRODUCTIVE TOXICITY

Human sperm was exposed to solutions containing 0.3, 3, 30, 300 and 3,000ppm H_2O_2 *in vitro*. In unwashed spermatozoa, the ED_{50} (the concentration that results in a 50% reduction of the mobility index of spermatozoa) of H_2O_2 was between 30 and 300ppm (Wales *et al*, 1959). Removal of endogenous catalase by washing increased the toxicity of H_2O_2 to spermatozoa.

9.12 NEUROTOXICITY

No information is available.

9.13 EVALUATION

Accidental exposure to H_2O_2 has occurred from its use in household topical disinfectants and cosmetic/personal care products. Young children are particularly vulnerable to accidental oral exposure. Deaths have been reported from ingestion of unknown quantities of 30-40% solutions. The effects seen were related to a corrosive action on the gastro-intestinal tract and to generation of large volumes of oxygen. Complete recovery has occurred in near fatal cases within 2-3 weeks with medical care.

H_2O_2 solutions of 1-3% have been used as anti-bacterial agent in the eye and mouth washes without causing significant injury. In the eye, H_2O_2 solutions of >200ppm caused hyperemia; pain and stinging occurred with concentrations of ≥100ppm.

In volunteers exposed to aerosol for 4h, the irritation threshold for the respiratory tract was 10mg/m^3 H_2O_2 and for the skin 20mg/m^3. At these concentrations, eye and throat irritation and gradual bleaching of hair has been reported. At concentrations at or below the present occupational exposure limit of 1.4mg/m^3 only hair bleaching was observed; this may, however, also have been caused by H_2O_2 transferred from the hands to the hair.

SECTION 10. FIRST AID AND SAFE HANDLING ADVICE

This section has been based on Material Safety Datasheets from L'Air Liquide (1990b-j), Amylum (1990), Atochem (1989a-e, 1990), Degussa (1986, 1988, 1989), Du Pont (1990a,b), Eka Nobel (1986a-c, 1988a,b, 1989), FMC (1990a-d), Mallinckrodt (1989), Montefluos (1990a-c) and Solvay (1984a,b), and on information from CEDRE (1990) US DOT (1987) and Weiberg and Leuchtenberger (1978).

10.1 FIRST AID AND MEDICAL TREATMENT

This advice applies to all commercially available grades of H_2O_2 solutions (3-70%), unless stated otherwise.

10.1.1 First Aid

Eye contact. Immediately flush eyes with plenty of water for at least 15 minutes (keep eyelids apart). Seek medical attention; with ≤5% solutions, medical attention is required only if irritation or burning sensation persists.

Skin contact. Remove contaminated clothing and shoes. Soak contaminated clothes in water to prevent risk of fire. Wash contaminated skin with water for at least 15 minutes. Keep patient warm and quiet. Seek medical attention. With a ≤5% solution, medical attention is required only if irritation or ulcers develop.

Inhalation. Move subject to fresh air and keep warm and quiet. If not breathing, give artificial respiration. Obtain medical attention immediately.

Ingestion. Do not induce vomiting. Flush mouth with water. Give several glasses of water to drink if subject is conscious. Keep subject quiet and warm. Seek medical attention.

10.1.2 Notes to Physicians

H_2O_2 solutions and their vapours and airborne mists are of low toxicity, but, depending on the concentration and duration of exposure, may cause mild (≤5% solutions) to severe damage to the skin and mucous membranes. Symptoms will subside after exposure ceases except for highly concentrated solutions (≥70%) when symptoms are likely to persist. It is often difficult to estimate the amount of H_2O_2 ingested or the concentration of H_2O_2 solutions.

Eye contact. Stinging and burning sensation of the eyelids and conjunctivitis occur with 5% solutions and with vapours. Direct contact with 8% solutions may cause burning of the eyelids, keratitis; necrosis of mucous membranes, ulceration of the cornea. Appearance of

damage, even corneal ulceration, may be delayed for hours or days after an initial (false) healing period.

Following first aid, instil 1-2 drops of an anaesthetic or apply local corticosteroids. Keep subject under surveillance for 1-2 weeks.

Skin contact. Contact on a burn or open skin may cause a stinging or burning pain. A short period (2-3h) of whitening may occur at the point of contact, followed by redness, blisters, deep cutaneous necrosis. If large areas of skin are affected, the subject may suffer from shock. Treat as for thermal burns. No adverse effects are expected from dilute (≤5%) solutions on intact skin.

Inhalation. Effects depend on vapour or aerosol concentration and may include irritation of the nose, eyes and throat. Coughing, dyspnoea, shortness of breath may occur and, in the worst cases, there is a risk of lung oedema.

Ingestion. Ingestion may produce a burning sensation in the throat, oesophagus and stomach, abdominal pain, vomiting and diarrhoea. High concentrations may produce buccal foaming, micro-haemorrhage of the gastric mucosa with risk of micro-embolism. Blood-stained vomit, glottis oedema and shock may occur in severe cases.

Do not induce vomiting because of the danger of aspiration of foam. Prevent and treat shock, treat digestive tract burns. Large amounts of oxygen may rapidly be released from H_2O_2. Severe distension may be treated by flexible nasogastric or orogastric tube. Evacuation of the stomach by emesis induction or gastric lavage should be avoided.

10.2 SAFE HANDLING

General precautions.

Protect against heat.

Work in strictly clean areas and use only the minimal quantity necessary in the workplace.

All installations, containers and equipment must be made of completely pure materials compatible with H_2O_2 (section 3.2) and provided with the necessary devices to avoid pressure build-up, such as pressure relief valves and/or bursting discs, these should release to a safe area.

The design and operation of the system should ensure that no contamination can enter it. If a breather vent or similar device is used it should be provided with a filter to avoid any airborne contaminants entering the H_2O_2 system.

Depending upon the quantity of product being stored/handled, additional venting may be required by means of a ventable lid.

All materials must be cleaned before coming into contact with H_2O_2 according to the suppliers recommendations. Vessels and other ancillary items used for H_2O_2 handling should be exclusively reserved for this purpose. Never return unused solution to containers of H_2O_2.

When emptying plastic containers the preferred methods are syphoning or pumping, pressure should not be used. For stronger containers, pressure may be used, but only good quality air (or nitrogen), free from oil and other airborne contaminants, should be used.

Never confine H_2O_2 between two valves.

Personnel protection. Personnel must be educated in the hazards of H_2O_2 and that it slowly decomposes. Contamination causes the decomposition to take place at a much enhanced rate, and can be initiated even with trace amounts (a few ppm) of transition metal ions, and pH changes. Other factors such as direct sunlight and high temperatures can also lead to decomposition.

Decomposition results in a rapid increase in the rate of gas (plus steam) production which can lead to a pressure build up and bursting of the container if adequate relief is not provided.

H_2O_2 at strength >8% is an oxidising substance, having the potential to ignite combustible materials. Evaporation of water, e.g. by heat, may increase the concentration of a H_2O_2 solution, the higher the strength of the solution the greater is the potential for ignition.

When handling solutions of <8%, normal work clothing can be worn with impervious gloves, apron and shoes as well as eye protection. For stronger solutions, wear a non-flammable worksuit made of natural rubber, neoprene, nitrile rubber or PVC, including gloves, boots, trousers, jacket, and hood.

Leather shoes should not be worn as these can ignite within a few minutes of contact with H_2O_2. Cotton clothing can also ignite quickly. Protective skin creams offer no protection from H_2O_2.

Eye protection using chemical safety goggles must be worn when handling H_2O_2. In addition, a face-shield is desirable to protect against accidental splashing.

Safety showers and eye fountains must be provided at the work place, in addition sufficient clean water should be provided to deal with spillages.

Respiratory protection should be provided by natural or general ventilation of the workplace, with local exhaust points, where necessary, to control mists or vapours. Where there is a potential for airborne exposure in excess of applicable limits (section 5.2), a face-mask with an approved cartridge must be provided, used as an escape mask. In cases of severe exposure, e.g. in dealing with an emergency, self-contained breathing apparatus should be used by qualified personnel.

Storage. Store H_2O_2 solutions outside in a cool, clean place or in clean, well ventilated rooms, built with non-combustible materials. Do not stack containers next to the air vents. The floors should be impermeable so that when accidental leakage occurs, the product will flow away to a safe area or be retained.

Do not store on wooden pallets. Store away from reactive substances (e.g. finely divided metals and their salts, strong acids and alkalis, organic substances, oils and greases) and combustible materials (e.g. straw, paper, wood, textile), and heat sources.

Containers should be regularly checked for signs of abnormality, e.g. bulging or increased temperature. Regularly verify the availability of ample supply of water for emergencies. For bulk storage, the supplier should be consulted regarding the design and installation.

10.3 MANAGEMENT OF SPILLAGE AND WASTE

Spillage. In the event of a container spillage, evacuate and isolate the hazard area and keep people away, stay upwind and keep out of low-lying areas. Contain the spill, if possible, and dilute with large amounts of water before disposal. If containment is not possible wash down with copious amounts of water. If water pollution occurs, notify the appropriate authorities.

If containers are involved in a fire situation, drench with water, keep adjacent containers cool by spraying with water. These operations should only be undertaken by personnel equipped with fire fighting protection. For bulk storage spillages, a pre-arranged plan must be worked out in conjuction with the supplier and the competent authority, if applicable.

Waste disposal. In most countries, there will be statutory regulations governing the disposal of H_2O_2. Solutions containing <1% can normally be flushed down drains (no explosion hazard); in certain cases it may need to be more dilute.

For further and more detailed safety instructions, contact your H_2O_2 supplier.

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Joint Assessment of Commodity Chemicals No. 22, Hydrogen Peroxide

Errata (4 October 1994)

Page 7, Table 1: 45% should read 35%, density should read 1,133.
Density: decimal points should be read as comma's.

Page 16, Section 4.1.1 Suface water. The second and third reaction should be equated electrically: $Org^* + O_2 \rightarrow Org^{\cdot +} + \cdot O_2^-$

$$2 \cdot O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

In seawater, similarly, the reactions should read:

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + \cdot O_2^-$$

$$Fe^{2+} + \cdot O_2^- + 2H^+ \rightarrow Fe^{3+} + \cdot O_2^-$$

Page 36, Table 11: Concentrations measured by Kaelin *et al* without ventilation other than the windows were 41 mg/m^3 on the floor and 12 mg/m^3 close to the machine; with new ventilation the respective values were 4.5 mg/m^3 and 1.5 mg/m^3.

Page 40, Table 13: µg/l should read mg/l

Page 33, Section 5.2.1: The second sentence should be replaced by:

"It is generally only permitted ... chemical means. The residual level in food immediately after aseptic packaging should not exceed 0.5 ppm (US FDA, 1990). Under the GRAS regulation, the maximum treatment levels for H_2O_2 in food applications can be up to 1.25% depending on the use (US FDA, 1992)."

References:

US FDA (US Food and Drug Administration) (1992). Maximum usage levels permitted [in food]. CFR 21, 184.1366c.

US FDA (US Food and Drug Administration) (1990). Substances utilized to control the growth of microorganisms. CFR 21, 178.1005d [unchanged in 1993 edition].

Page 54/55, Table 20 Please insert the attached table.

Page 69, Gavage: calculated, based on 0.5% should read 5% solution

Page 140: ATOCHEM should read ELF ATOCHEM and A. MAYR should read W. MAYR.

Encl. Table 20

Table 20: Enzymatic Activity in Organs and Tissues of Rats (Matkovics and Novak, 1977)

Organ or tissue	Enzymatic activity (U/g wet weight)					
	Superoxide dismutase		Peroxidase		Catalase	
	Controls	H_2O_2-treated	Controls	H_2O_2-treated	Controls	H_2O_2-treated
Organs						
Liver	4,000 ± 600	10,408 ±750	0	0	4.80 ± 0.43	25.250 ± 2.455
Kidney	1,120 ± 151	1,692 ±240	361 ± 33	1,200 ± 105	0.36 ± 0.03	3.300 ± 0.295
Spleen	560 ± 50	470 ±240	963 ± 91	4,250 ± 418	2.40 ± 0.21	0.730 ± 0.062
Testes	960 ± 63	1,100 ± 53	407 ± 41	-	0.41 ± 0.03	0.150 ± 0.011
Whole brain	240 ± 24	397 ± 38	120 ± 10	140 ± 13	0.04 ± 0.004	0.012 ± 0.001
Lung	210 ± 20	895 ± 85	872 ± 86	2,020 ± 201	0.26 ± 0.02	0.520 ± 0.050
Pancreas	310 ± 31	352 ± 33	136 ± 13	460 ± 46	0.195 ± 0.010	0.255 ± 0.023
Muscles						
Heart	480 ± 47	950 ± 93	2,690 ± 300	1,615 ± 155	0.245 ± 0.023	0.725 ± 0.065
Skeletal	300 ± 27	530 ± 50	105 ± 10	750 ± 69	0.11 ± 0.009	0.092 ± 0.009
Haemolysate*	696 ± 68	787 ± 80	11,666 ± 1,000	17,900 ± 1,340	4.12 ± 0.04	6.98 ± 0.07

* U/ml wet weight; n = 10; catalase activity-values in U/g wet weight