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Toxicological evaluation of *Sany Safe*

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Executive Summary

It is here reported a toxicological evaluation of the disinfection liquid used in the *SANY SAFE* sanitizing nebulizer by considering its intended use (declared by the producer) and based on the available literature. The vendor of this product is AVS Electronics S.p.a. via Valsugana, 63, 35010 Curtarolo (PD) – ITALY. All the compositional data and the instructions for a correct use of this product were supplied by the vendor.
It was carried out a bibliographical evaluation of the potential skin irritating, sensitizing, and ocular and inhalation effects of the substances declared to be vaporized by the *Sany Safe* device. This document neither comments nor evaluates the effectiveness sanitization ability in real contexts of the *Sany Safe* device, for this it is possible to refer to the specific documentation produced by the vendor.

Product to be evaluated

The liquid here considered is a clear colourless liquid contained and sold in tanks of different volumes (5, 10 and 25 dm^3). The density of the liquid is 0.99 g/cm^3.
The liquid is an aqueous solution of two disinfectants with bactericidal/virucidal activity (i.e. with the capacity to or tending to inactivate/damage bacteria and viruses) proposed for the sanitization of indoor spaces. The vendor declares that the vaporized liquid by *Sany Safe* contains:

- 7% $_{w/w}$ Ethanol (CH_3CH_2OH)
- 6 % $_{w/w}$ Hydrogen Peroxide (H_2O_2)
- 87% $_{w/w}$ demineralised water

Effectiveness of the components of the liquid vaporized by *Sany Safe*

The two active components of the liquid vaporized by *Sany Safe* (ethanol and hydrogen peroxide) have - on the basis of the actual literature - bactericidal/virucidal activity. The chemical properties of ethanol and hydrogen peroxide give to these compounds the ability to interact with pathogens inactivating and damaging viruses and bacteria.

Toxicological evaluation of *Sany Safe*

As declared by AVS Electronics Spa the composition of the mixture to be used in the *Sany Safe* device is reported in Table 1.

Table 1. Composition of the liquid used in the *Sany Safe* device as declared by the vendor.

Substance	CAS #	Percentage in the preparation w/w
Water	7732-18-5	87
Ethanol	64-17-5	7
Hydrogen Peroxide	7722-84-1	6

The vendor suggested different dosages as a function of the type of disinfection to be obtained (low, medium and high sanitization) and as a function of the dimension of the room where the device should be installed. The different type of sanitization corresponds to a different frequency for the treatment

- Low sanitization: once a day

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- Medium sanitization: 3 times per week
- High sanitization: once a week

The dosage of liquid vaporized is also function of the type of sanitization to be obtained:

- Low sanitization: 1 g of liquid vaporized per treatment per cubic meter
- Medium sanitization: 3 g of liquid vaporized per treatment per cubic meter
- High sanitization: 10 g of liquid vaporized per treatment per cubic meter

The released amount of each components in the 3 different sanitization conditions for each cycle of sanitization per cubic meter of room is reported in Table 2, together with the overall vaporized amount of each component for a typical 100 m^3 room (as suggested by the vendor).

Table 2. Suggested vaporized amount for each compounds per sanitization step per cubic meter. Amount of vaporized compounds per sanitization step for a 100 m^3 room.

Substance	Mass of each compound per sanitization dose (g/m^3)	Mass of each compound per sanitization dose for a 100 m^3 room (g)
Low sanitization		
Water	0.924	92.4
Ethanol	0.07	7
Hydrogen Peroxide	0.06	6
Medium sanitization		
Water	2.772	277.2
Ethanol	0.21	21.0
Hydrogen Peroxide	0.18	18.0
High sanitization		
Water	9.24	924
Ethanol	0.7	70
Hydrogen Peroxide	0.6	60

By considering the intended use of the solution object of the present toxicological evaluation the potential routes of exposure for the human are: skin contact, eye contact, inhalation and intentional ingestion. So, a bibliographic search regarding the potential oral and eyes sensitizing, skin irritating and inhalation effects of the each component was carried out through reliable public databases (mainly the PubChem[1] and PubMed databases[2]) and in primary scientific literature trough Scopus and WebOfScience databases.

The toxicological aspects of the ingredients of the solution evaporated by *Sany Safe* were evaluated for each component separately. No interaction and synergistic effects between ingredients was considered. No toxicological evaluation of the possible by-products obtained for the chemical transformation of the ingredients once vaporized in indoor spaces was carried out.

It is not possible to accurately evaluate the human assumption of the single ingredients of the mixture through the identified routes of exposure. However, on the basis of some general hypothesis a rough and conservative estimation of the possible maximum assimilation can be done. Taking into account an average inspired air volume of 8 dm^3 per minute, and the maximum dose suggested for indoor decontamination (10 g of product per cubic meter for each treatment to have the highest sanitization degree), a reasonable estimate of the maximum inhaled quantity is 80 mg per minute of the whole mixture. For 1 hour exposure the maximum inhaled quantity of the various ingredients is reported in Table 3, taking into account a total volume of air inhaled of 480 dm^3 and under the hypothesis that all the amount inhaled will deposit onto the respiratory apparatus and no decrease of the concentration takes place during the exposure time (no transformation of the compounds in by-products, no partitioning on the surface of the room...).

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Table 3. Estimation of the maximum amount of inhaled substance in one hour in the case of High Sanitization (10 g per cubic meter of the vaporized *Sany Safe* solution). Estimation of the inhaled air per hour = 480 dm^3. The LD50 for hydrogen peroxide from [3].

	Ethanol	*Hydrogen Peroxide*
max inhaled dose, mg	336	290
Estimated LD50 (70 kg bw)	350,000	35,000-39,200

Risk for human and animal health

The maximum inhaled dose estimated and reported in Table 3 is roughly 3 orders of magnitude for ethanol and 2 orders of magnitude for hydrogen peroxide lower than the estimated acute toxicity levels (LD50 by considering a body weight equal to 70 kg). As a consequence, with the current knowledge my conclusion is that the vaporized solution used in the *Sany Safe* device, if used as suggested, does not represent a threat (acute) for human and animal health for a single episode of 1 hour exposure.
The compounds vaporized by *Sany Safe* (water, hydrogen peroxide and ethanol) can be involved in chemical reaction with formation of potential by-products. This report, as underlined above, does not consider the toxicology of the potentially formed by-products. As suggested by the vendor, it is strongly suggested the ventilation of the room at the end of the sanitization. Conversely, mild irritation to the eyes can presumably occur.

Ethanol (CAS # 64-17-5)

Ethanol (also called ethylic alcohol or simply alcohol) is a volatile compound, flammable and colourless. It is well known for its psychoactive properties and it is a common ingredients found in alcoholic drinks. Ethanol can be produced by the fermentation of sugars or through petrochemical processes. Ethylic alcohol finds a huge use both in the chemical industry and as a popular recreational drug (e.g. in drinks obtained from fermentative processes such wine and beer).
It has also applications in medicine as antiseptic, disinfectant, and antidote. In particular, it is applied to the skin as common disinfectant used either in water solution at different concentrations (the better disinfection ability is at 65-80 %) or in sanitizer gel for the removal of pathogens from the skin.

Toxicity Summary[4]

HUMAN STUDIES: Ethanol is a central nervous system (CNS) depressant. It enhances the inhibitory effects of gamma-aminobutyric acid (GABA) at the GABA-A receptor and competitively inhibits the binding of glycine at the N-methyl-d-aspartate receptor (it disrupts excitatory glutaminergic neurotransmission). Ethanol also stimulates release of other inhibitory neurotransmitters, such as dopamine and serotonin. The most common clinical signs of ethanol toxicosis are ataxia, lethargy, vomiting, and recumbency. In more severe cases, hypothermia, disorientation, vocalization, hypotension, tremors, tachycardia, acidosis, diarrhea, respiratory depression, coma, seizures, and death may occur. Alcohol is directly irritating to the stomach and causes vomiting. High ethanol blood levels also stimulate emesis. The concern with vomiting during intoxication is that at high blood ethanol concentrations, the muscles that control the epiglottis become slow to react or even paralyzed. This increases the risk for aspiration. Ethanol intoxication reduces peripheral oxygen delivery and metabolism and causes mitochondrial oxidative dysfunction, potentially resulting in shock or hypoxia in an acutely intoxicated patient. Hypothermia may result from multiple mechanisms. Peripheral vasodilation, CNS depression, ethanol interference with the thermoregulator

mechanism, and/or impaired behavioural responses to a cold environment all lead to a lowered body temperature. Moderate ethanol intake appears to reduce the risk of myocardial infarction and other heart diseases. However, high spirits consumption was associated with increased risk of cancer mortality in women. Consumption of alcoholic beverages (beer, in particular) is associated with an increased risk for rectal but not colon cancer. Beer is a commonly consumed alcoholic beverage among reproductive-age adults. Beer drinking males have an increased risk of contributing to pregnancy waste. Women consume beer before and after pregnancy recognition. Binge drinking appears to be a common drinking behaviour, and those who binge drink have an increased risk of impaired foetus growth and offspring behaviour. Beer consumption by lactating women might temporarily impair motor function of nursing infants. The rate of ethanol metabolism varies among individuals. Studies of twins indicate that interindividual variability in the rate of ethanol metabolism may be genetically controlled. The main pathway for ethanol oxidation in humans is to acetaldehyde via alcohol dehydrogenase pathway. Acetaldehyde is oxidized further to acetic acid by aldehyde dehydrogenase. Asians are known to be sensitive to the health effects of ethanol; the sensitivity has been attributed to different forms of the enzyme acetaldehyde dehydrogenase. Alcohol ingestion by Asians resulted in marked elevations of blood acetaldehyde levels ranging from 0.4 to 3 mg/L, and individuals developed facial flushing and tachycardia as a direct consequence of elevated blood acetaldehyde levels. ANIMAL STUDIES: A drop full-strength ethanol on rabbit eyes causes reversible injury graded only 3 on a scale of 10 after 24 hr. Application of 70% alcohol to rabbit corneas injures and temporarily loosens the corneal epithelium, but the recovery is complete. When rats were dosed with ethanol by oral gavage with 8 to 15 g/kg/day over 4 months and fed a diet containing 25% of total calories as fat, focal necrosis, inflammation, and fibrosis were observed in the liver. Nine baboons fed ethanol at 50% of total calories developed fatty liver, and four animals developed hepatitis within 9 to 12 months. Rabbits exposed to saturated vapours of ethanol for periods ranging from 25 to 365 days developed cirrhosis of the liver. Rats were given a single intraperitoneal dose of diethylnitrosamine followed by treatment with ethanol in drinking water for 12 to 18 months. Ethanol was an effective promoter of liver tumours. Cynomolgus monkeys administered up to 5 g/kg bw ethanol daily on gestation days 20-150 revealed an increase in pregnancy wastage (abortions and still births) but no structural malformation or facial change. Ethanol, and not acetaldehyde, has been implicated as the causative agent of the teratogenic effects in laboratory animals. Oral coadministration of 100 mg/kg of 4-methylpyrazole, an inhibitor of alcohol dehydrogenase, with 6 g/kg of ethanol intraperitoneally on gestation day 10 dramatically increased the embryotoxicity of ethanol in mice. Ethanol is not mutagenic in Salmonella typhimurium strains TA 97, TA 98, TA 100, TA 1535, TA 1537, or TA 1538 in the presence or absence of metabolic activation. In the presence of a metabolic activation system, ethanol is slightly mutagenic to Salmonella strain TA 102, a strain considered to respond to the presence of oxygen radicals. Ethanol did not induce mutations in mouse lymphoma L5178Y TK+/- cells and did not induce micronuclei in Chinese hamster V79 cells in the absence of metabolic activation. No chromosomal aberrations or sister chromatid exchanges were observed in Chinese hamster ovary cells treated with ethanol. ECOTOXICITY STUDIES: The zebrafish were exposed to different concentrations (control, 0.01, 0.1, and 1%) of ethanol from blastula stage to 144 hour-post-fertilization (hpf). No effect on survival was observed except the 1% ethanol group suffered 89% mortality during 108-120 hpf. No developmental defects were observed at the 0.01 and 0.1% concentrations, but significantly higher deformity rates occurred with 1% ethanol. Hyperactivity and less tortuous swimming paths were observed in all ethanol concentrations.

IRRITATION AND SENSITIZATION EFFECTS ON SKIN

Coetaneous reactions to ethanol, 1-propanol, 2-propanol and acetaldehyde were evaluated by Haddock et al in a control group and in patients before and while they were receiving disulfiram therapy.[5] Local coetaneous erythema was observed from parch tests with ethanol, 1-propanol and 2-

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propanol in hydrated skin, and from acetaldehyde in dry skin. Erythema resulting from topically applied alcohols occurred in a dose related manner and was caused by a direct vasodilatory effect on the coetaneous microvasculature.
Potential skin irritating effects of ethanol were investigated by Bingham et al.[6] Human subjects reported no apparent skin irritation when applied to the forearm of human subjects in a modified Draize test. No irritation was noted when ethanol was applied to the forearm openly for 21 days, whereas 21-days occlusive test caused erythema and in duration toward the end of the exposure period. There have been infrequent reports of skin sensitization reactions attributed to ethanol. Ethanol is a weak sensitizer in a patch test.
Non human toxicity values are reported below[4].
LD50 Mouse subcutaneous 8285 mg/kg
LDLo Dog subcutaneous: 6600 mg/kg
Ethyl alcohol was considered mildly toxic by skin contact.[4]

ORAL ADMINISTRATION

Falk M. et al administered orally to rats by means of an intragastric tube ethanol (0.6/100 g) in order to evaluate potential toxic effect of this alcohol. [4] The administration caused an accumulation of secretory vesicles laden with very low density lipoprotein (VlDL) particles which were seen 90 min after administration and later disappeared.
Pankov et al performed a single ethanol administration in rat. [4] In response to alcohol administration the catecholamine secretion from the adrenal medulla was enhanced as evaluated by urinary catecholamine excretion in rats. The threshold dose of 87 mmol/Kg also produced a transient increase in blood sugar concentration. Experiments with chronic ethanol treated rats showed that the increase of urinary catecholamine excretion following 87 mmol/Kg disappeared occasionally, whereas the increase following repeated administration of 130 mmol (Kg is permanent. Morphologic evaluation revealed enlargement of the adrenal medulla, changes of cells and nuclei as well as a distinct reduction of chromaffin reaction.

EFFECTS ON EYES

Grant *et al.* treated rabbit eyes with a drop of ethanol 96%[4]. The treatment caused reversible injury graded only 3 on a scale of 10 after 24 hours. Application of 70% alcohol to rabbit corneas injures and temporally loosens the corneal epithelium, but the recovery was complete. Repeated application (7 drops) of 40 to 80% alcohol to rabbit eyes over an unspecified but presumably longer time caused loss of corneal epithelium and endothelium, followed by haemorrhages in the conjunctiva, and infiltration and vascularisation of the corneal stroma.

INHALATION EFFECTS

The effects of inhalation exposure to ethyl alcohol were studied by Bingham et al[4]. In a nontolerant human subject, the inhalation exposure to 1380 ppm ethanol for 39 min resulted in no effects at 28 min, but headaches and slight numbness at 33 min. At 3340 ppmv for 100 min, sensation of warmth and coldness, nasal irritation, headaches and numbness were reported. When exposed to 8840 ppmv for 64 min, the subjects complained of a momentary intolerable odour and difficulty in breathing, conjunctival and nasal irritation, a feeling of warmth, headache, drowsiness and fatigue. In tolerant individuals, the symptoms are less severe, and the time required to produce them is greater than in intolerant individuals. For instance, a human subject tolerant to alcohol reported slight headaches after 20 min exposure to 5030 ppmv for 120 minutes. Intoxication has been seen among humans subjected to inhalation of vapours from hot alcohol.

In a study reported by Grant[4], alcohol vapour exposure at sufficiently high concentration may cause prompt stinging and watering of the eyes, but there appear to be no reports on eye injury from industrial exposure to alcohol vapours. Human volunteers exposed to alcohol vapour have observed at concentrations of 0.7 to 1% vapour in air the smell of alcohol was at first unbearable, although unpleasant later, and that the eyes began to burn with increased intensity after several minutes. A vapour concentration of 0.25% (2500 ppmv) had no notable effect on the eyes.

Non Human and Human acute toxicity (oral, inhalation)

Non Human toxicity values are reported below.[4]
LD50 Mouse iv 2.0 g/L
LD50 Mouse sc 8.3 g/L
LD50 Mouse ip 0.9 g/L
LC50 Mouse inhalation 39 g/m^3/4 hr
LD50 Mouse oral 3.4 g/L
LD50 Rat iv 1.4 g/L
LD50 Rat ip 3.8 g/L
LC50 Rat inhalation 20000 ppm/ 10 hr
LD50 Rat oral 7.0 g/L
LD50 Rat oral 10.6 g/kg
LD50 Guinea pig oral 5.6 g/kg
LD50 Rat oral 9.9 g/kg
LD50 Rat (young adult) oral 17.8 g/kg
LD50 Rat (14 days old) oral 6.2 g/kg
LD50 Rat (older adults) oral 11.5 g/kg
LD50 Dog oral 5.5 g/kg

Human toxicity values are reported below:
LDLo Infant (0-1 year) subcutaneous: 7060 mg/Kg
LDLo Human oral: 1400 mg/Kg
LDLo Child (1-13 years): 2000 mg/Kg
TDLo Man oral: 700 mg/Kg
TDLo woman oral: 256 g/Kg/12 weeks

Hydrogen Peroxide (CAS# 7722-84-1)

Hydrogen peroxide (H_2O_2) is a chemical compounds usually commercialized as aqueous solutions. It finds different applications such as bleaching agent, oxidizer and antiseptic.
The uses of hydrogen peroxide are strictly related to its redox properties, in particular in acidic pH is a powerful oxidizer that can be use as alternative to the more dangerous chlorine, chlorine dioxide and potassium permanganate. Almost 60% of the overall production of hydrogen peroxide is used in the paper industry for pulp- and paper-bleaching. Furthermore, it is used also in waste water treatment processes especially for the removal of biorecalcitrant organic pollutants (e.g. in the so called Fenton process).
H_2O_2 is also used for the sterilization of surfaces, such as surgical tools.[7] Furthermore, it is used in the form of vapour for room sterilization. Its efficacy has been demonstrated against viruses, bacteria, yeasts, and bacterial spores.[8] Falagas *et al.* published in 2011 a quite complete review of the potential applications of hydrogen peroxide for the disinfection of the hospital environment, concluding that *i*) airborne hydrogen peroxide, either in the form of vapour or dry mist, can be an effective method for

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the disinfection of the hospital inanimate environment; *ii*) Complete or almost complete disinfection of the sampled hospital sites was achieved with airborne hydrogen peroxide; *iii*) Disinfection of the hospital environment using airborne hydrogen peroxide can have important advantages; *iv*) Hydrogen peroxide is a broad-spectrum disinfectant, considered active against the majority of pathogens implicated in nosocomial infections.[9]

Toxicity summary

Hydrogen peroxide causes toxicity via three main mechanisms: corrosive damage, oxygen gas formation and lipid peroxidation.[10]
H_2O_2 is an endogenous product of oxygen reduction in the aerobic cell and passes readily across biological membranes. At high-uptake rates H_2O_2 can pass the absorption surface entering the adjacent tissues and blood vessels where it is rapidly degraded by catalase liberating oxygen bubbles; consequently, mechanical pressure injury and oxygen embolism may be produced. Due to the high-degradation capacity for H_2O_2 in blood it is unlikely that the substance is systemically distributed, and therefore the endogenous steady state levels of the substance in tissues are unlikely to be affected.[3]
Absorbed hydrogen peroxide is very rapidly broken down by enzymes, including glutathione, peroxidise or catalase in tissue and hence does not give rise to systemic toxicity. Formation of hydroxyl radicals in cells of tissues of first contact may induce lipid peroxidation, DNA damage and cell death.[11] and references therein

Dermal and Ocular exposure

Concentrated hydrogen peroxide is caustic and exposure may result in local tissue damage.
Ocular exposure to 3% solutions may cause immediate stinging, irritation, lacrimation and blurred vision, but severe injury is unlikely. Exposure to more concentrated hydrogen peroxide solutions (>10%) may result in ulceration or perforation of the cornea.[10]
Ocular exposure to hydrogen peroxide solutions of greater than 35 % are expected to cause corrosion, corneal burns, lacrimation, photophobia, conjunctivitis and permanent injury including blindness. [11] and reference therein
Dermal exposure to dilute solutions of hydrogen peroxide cause whitening or bleaching of the skin due to microembolism caused by oxygen bubbles in the capillaries. Dermal contact with solutions of 35 % hydrogen peroxide cause mild skin irritation. Solutions of 50 % hydrogen peroxide and above cause severe irritation and corrosion, severe burns, blisters, ulcers and permanent scarring.[11] and reference therein

Oral administration

Acute ingestion of hydrogen peroxide results in gastrointestinal irritation, and possible gas embolism. Concentrations greater than 30 – 40 % cause severe irritation, with signs and symptoms including abdominal pain, foaming at the mouth, vomiting and haematemesis, and gastric distension. Fever, lethargy, shock, unconsciousness and respiratory arrest may also occur. Concentrated solutions may cause gas embolism, and in severe cases, death may occur within minutes of ingestion. However, most cases of acute ingestion of hydrogen peroxide result only in mild adverse effects. [11] and reference therein, 10

Ingestion of concentrated (>35%) hydrogen peroxide can also result in the generation of substantial volumes of oxygen. Where the amount of oxygen evolved exceeds its maximum solubility in blood, venous or arterial gas embolism may occur. The mechanism damage is thought to be arterial gas embolisation with subsequent brain infarction. Rapid generation of oxygen in closed body cavities can also cause mechanical distension and there is potential for the rupture of the hollow viscous secondary to oxygen liberation. In addition, intravascular foaming following absorption can seriously

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impede right ventricular output and produce complete loss of cardiac output. Hydrogen peroxide can also exert a direct cytotoxic effect via lipid peroxidation.[10]

INHALATION EFFECTS

Hydrogen peroxide does not readily form a vapour at room temperature. However, if heated or misted, acute inhalation of hydrogen peroxide will cause irritation to the nose, throat and respiratory tract. Dyspnoea and cough have also been reported [12]. In very severe cases bronchitis or pulmonary oedema may occur, which can potentially be fatal. In human volunteers exposed to an aerosol of hydrogen peroxide for 4 hours, the threshold for respiratory tract irritation was 10 mg m^{-3}. [11 and reference therein]

Although most inhalational exposures cause little more than coughing and transient dyspnoea, inhalation of highly concentrated solutions of hydrogen peroxide can cause severe irritation and inflammation of mucous membranes, with coughing and dyspnoea. Shock, coma and convulsions may ensue and pulmonary oedema may occur up to 24-72 hours post exposure. Severe toxicity has resulted from the use of hydrogen peroxide solutions to irrigate wounds within closed body cavities or under pressure as oxygen gas embolism has resulted. Inflammation, blistering and severe skin damage may follow dermal contact.[10]

ACUTE TOXICITY [3]

The oral LD50 values or lethal doses in rats range between 800 mg/kg for 70% H_2O_2 to more than 5,000 mg/kg for 10% H_2O_2. The mechanism of systemic effect has been oxygen embolism. Thus, the substance proved to be harmful if swallowed by a physical mode of action.
The dermal LD50 values in animals range between 700-5,000 mg/kg for 90% H_2O_2. The test methods are mostly poorly described, but the studies indicate that H_2O_2 is not acutely toxic after skin application.
Acute inhalation toxicity studies have been performed with aerosols (mice) and vapours (rats and mice). Due to the corrosive nature of the substance after inhalation exposures to highly concentrated aerosols (70% H_2O_2 as “droplets”), lethality occurs at quite low air concentrations of this substance (0.92-2 mg/dm^3). The lethal event can be attributed to the substance corrosivity rather than its systemic toxicity. A marked difference in susceptibility to H_2O_2 between mice and rats after inhalation uptake of vapours may be deduced from the available studies. In mice, vapour concentrations of up to 0.3 mg/dm^3 for 4 hours caused death of at least half of the animals within 2 weeks. In rat studies, no mortality was observed at comparative exposure concentrations. The substance is considered to be harmful by inhalation.

LONG TERM EFFECTS

Mutagenicity[3]

H_2O_2 is a mutagen and genotoxicant in a variety of *in vitro* test systems. Regarding *in vivo* genotoxicity, studies have explored DNA repair in liver cells of rats, as well as micronucleus formation in mice, all with a negative outcome. At low concentrations (0.2-3.2% solutions), and with a low application frequency on the skin of mice, H_2O_2 did not induce local genotoxicity or mutagenicity. The available studies are not in support of significant genotoxicity/mutagenicity of H_2O_2 under *in vivo* conditions.

Carcinogenicity

Although 0.1-0.4% H_2O_2 in drinking water showed potential to induce local carcinogenic effects in the duodenum of a sensitive, catalase-deficient mouse strain, it is notable that the lesions showed a marked tendency of regression and even disappearance after the cessation of treatment. The

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mechanism of the carcinogenic effect is unclear. In rats, administration of H_2O_2 in drinking water was not associated with the occurrence of tumours. In another study, however, 1% H_2O_2 in drinking water induced squamous cell papillomas in the forestomach of rats. Tumour promotion studies with H_2O_2 revealed equivocal results. The special nature of the demonstrated carcinogenicity of H_2O_2, an endogenous reactive oxygen species, the existing biological defence mechanisms, and the overall evidence available, cast some doubt on whether H_2O_2 is a carcinogen of practical significance and the evidence is considered to be insufficient to trigger classification.[3]
In PubChem database[13] similar conclusions are reported for the carcinogenicity of hydrogen peroxide:

- There is inadequate evidence in humans for the carcinogenicity of hydrogen peroxide. There is limited evidence in experimental animals for the carcinogenicity of hydrogen peroxide. Overall evaluation: Hydrogen peroxide is not classifiable as to its carcinogenicity to humans (Group 3).[14]
- Confirmed animal carcinogen with unknown relevance to humans.[15]

Water (CAS# 7732-18-5)

Water is the most important biological fluid. The life in the Earth is strictly related to the availability of water in liquid form. As a consequence of its peculiar molecular properties it is the ideal solvent for the most important inorganic and organic species that support the life.
No real toxicological effect can be underlined for water in common conditions. The environmental Protection Agency (EPA) of USA categorized water with the green circle adopted for the chemicals that have been verified to be of low concern based on experimental and modelled data. Water itself is nontoxic and is in fact essential for life.

Oral administration

An over-administration of water can have some adverse effects as a consequence of the over-dilution of the biological fluids. Human systemic effects by ingestion of very large amounts are: body temperature increase, convulsions, diarrhea, fever, hypermotility, muscle contraction or spasticity, mydriasis, nausea or vomiting, tremors.[16]
Some other effects related to the exaggerated ingestion of water are reported in Table 4.

Table 4. Some adverse effects of the over-administration of water

Organism	Route	Dose	Effect	Reference
Infant	oral	333 g/kg	Behavioural: convulsion or effect on seizure threshold; gastrointestinal hypermobility, diarrhea	17
Man	oral	42.9 g/kg	Behavioural: tremor; behavioural: muscle contraction or spasticity	18

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