The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

116. Glyoxal

Per Lundberg
Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an Expert Group. At present the Nordic Expert Group consists of the following members:

Helgi Gadbergsson Municipal Institute of Public Health, Iceland
Petter Kristensen National Institute of Occupational Health, Norway
Per Lundberg (chairman) National Institute of Occupational Health, Sweden
Vesa Rihimäki Institute of Occupational Health, Finland
Adolf Schäft Fries National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxicol, Medline, Cancerlit and Niosh. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

An editorial work is performed by the Group's Scientific Secretary, Brita Beije, at the National Institute of Occupational Health in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m³ and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on Glycerol was made by Per Lundberg, PhD, National Institute of Occupational Health, S-171 84 Solna, Sweden. The final version was accepted by the Nordic Expert Group, October 20, 1994, as its document.

Brita Beije
Scientific Secretary

Per Lundberg
Chairman
1. Introduction

This criteria document on glyoxal was requested from Finland. There is an increased use of glyoxal in the paper industry in coating baths for offset and special papers. There is also an increased use for glyoxal in the crude oil and gas industry as a deodorising agent (H₂S scavenger). There are no occupational exposure limit values for glyoxal in the Nordic countries at present. The reactivity of the compound and the increased industrial use makes an evaluation of the health risks needed, especially as other low-molecular aldehydes, such as formaldehyde and acetaldehyde, are shown to be irritative and to have a carcinogenic potential.

2. Substance Identification

(data from refs 3, 24, 25, 46)

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Stereochemically glyoxal exists in a cis-form and a trans-form.

3. Physical and Chemical Properties

Some constants are given in Table 1. Data from (3, 24, 25, 46).

Glyoxal consists of yellow prisms or irregular pieces which turn white on cooling. The vapours are green and burn with a purple flame. It polymerises violently on contact with water or when dissolved in solvents containing water. The anhydrous polymer changes to the monomer upon heating (46).

Water solutions are acidic. A 40 % solution has a pH-value of 2.1-2.7. This commercially available solution may contain polymerisation inhibitors. Glyoxal has a weak sour odour.

Conversion factors: 1 mg/m³ = 2.41 ppm
                       1 ppm = 0.415 mg/m³
Table 1. Some physical and chemical data for glyoxal.

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* The vapour pressure at 20 °C has also been reported to be 220 mm Hg (15.3 kPa) (3).

4. Occurrence, Production and Use

Glyoxal is usually prepared by oxidation of acetaldehyde by nitric or selenium acid. It can also be prepared by hydrolysis of dichlorodioxane or by oxidation of ethane-1,2-diol with oxygen in the presence of water (46). The product is commonly supplied in the form of a 40% (wt/wt) solution in water.

Glyoxal is used in textiles, organic synthesis, glues, biocides, permanent-press fabrics. It is also used as an insolubilizing agent for compounds containing polyhydroxyl groups (such as polyvinyl alcohol, starch and cellulose materials). Glyoxal is also used as an insolubilizing agent for proteins (casein, gelatine and animal glue), in embalming fluids, in leather tanning, in paper coatings with hydroxyethylcellulose, as a reducing agent in dyeing textiles and as a cosmetic ingredient and dye intermediate (25).

The world production of glyoxal in 1991 was approximately 100,000 tonnes. Sweden imports about 400 tonnes glyoxal yearly. This is mainly used as disinfectant and preserving agent in the pulp industry.

Glyoxal has been identified in coffee and other beverages (15). Glyoxal is formed in irradiated sucrose solutions. This could be of importance in food preservation by ionizing radiation treatment (35, 36). Glyoxal is present in sea water and atmospheric air (26, 30).

5. Occupational Exposure Data

No data have been found in the literature about concentrations in the air at occupational settings.

6. Measurements and Analysis of Workplace Exposure

Glyoxal and other carbonyl compounds in marine air was sampled in volumes of 20 - 100 litres. The samples were pulled through a Teflon filter and one to three cartridges by a diaphragm pump at a flow rate of 200 - 1200 ml/min. Glyoxal and the other carbonyl compounds were trapped onto 2,4-dinitrophenylhydrazine and the hydrazone derivatives were separated by HPLC and detected by UV absorbance. Measurements of sub-ppt levels were possible (48).

Another method for the measurement of soluble atmospheric carbonyl compounds uses a pyrex cell gas-liquid scrubber sampler in conjunction with a HPLC equipped with a UV-visible detector for identification following derivatization with 2,4-dinitrophenylhydrazine. The detection limit for glyoxal is given to 0.01 ppt (30).

A method to determine glyoxal among other carboxylic acids and carbonyl compounds in estuarine and marine samples has been described (11, 26). After derivatization of 5 ml samples with 2,4-dinitrophenylhydrazine to form hydrazone, the separation is performed by HPLC on a RP-18 column by gradient elution and with UV-detection. The concentration of glyoxal was 4.0 - 12.0 µg/l and the detection limit 295 ng/l.

A thin-layer chromatographic method for the detection of glyoxal based on a fluorogenic reaction with o-aminodiphenyl has been reported. Glyoxal (1 µl of 1% solution) gives a marked violet fluorescence. The detection limit is reported to be 0.4 µg and the fluorescence is linear from 0.1 - 1.0 mg glyoxal per ml (31).

In a study from former Soviet Union a photometric method for determination of glyoxal in air from the working environment is presented (47). Neither the concentration of glyoxal nor the type of working environment is, however, stated in the report.

7. Toxicokinetics

7.1 Uptake

There are no data from the literature on uptake of glyoxal. From toxicity studies it can be assumed that glyoxal can be taken up through the skin and from the gastrointestinal tract. It should be noted that glyoxal polymerizes upon contact with water.

7.2 Distribution

There are no data in the literature concerning the distribution of glyoxal in the body.
7.3 Biotransformation

In the literature few data were found about biotransformation of glyoxal. In rat liver microsomes N-nitrosomorpholine has been shown to give glyoxal together with acetaldehyde, formaldehyde and N-nitroso-2-hydroxymorpholine (2).

In animal cells there is a glyoxalase system consisting of two enzymes. This system is capable of converting methylglyoxal to lactic acid via a thiolester (7). Whether this enzyme system can handle glyoxal has not been stated in the literature. In liver and erythrocytes of rats exposed to glyoxal an induction of both glyoxylase I and glyoxylase II was observed (44). In tissue extracts it has been shown that glyoxal can be anaerobically converted to glycolic acid when glutathione is added to the system. Glycolic acid can then be oxidised to glyoxylic acid by a soluble liver enzyme which reacts directly with molecular oxygen (29).

7.4 Elimination

There are no data in the literature on elimination of glyoxal.

8. Methods of Biological Monitoring

No methods of biological monitoring of glyoxal have been found in the literature.

9. Mechanism of Toxicity

Glyoxal is a very reactive compound. Inside a cell it can react with proteins, RNA and DNA, where it binds preferentially, due to its stereo structure, to guaninosine to form a relatively stable adduct (4, 22).

It has been suggested from studies with Salmoneella typhimurium that singlet oxygen formed from glyoxal is related to its mutagenicity (42).

The reaction of glyoxal with nucleic acid components has been studied. The reactions were followed spectrophoto metrically. The reactions of adenosine and cytidine with glyoxal were found to be reversible and the adducts were labile and could not be isolated from the reaction medium. On the other hand, the formation of the guanosine-glyoxal adduct was slower and the reaction product was much more stable (4). It has been shown that the formation of an adduct of glyoxal to the guanidinium ion occurs in two steps (10).

The reactions of glyoxal with nucleic acids, nucleotides and their bases have been examined by measuring spectral changes. The spectra of all bases and nucleotides in RNA and DNA were changed by treatment with high concentrations of glyoxal. When treated with a low concentration of glyoxal, however, only guanine or guanylic acid underwent a specific spectral change (32).

10. Effects in Animal and In Vitro Studies

10.1 Irritation and sensitisation

The effect of glyoxal (32.8 %, technical) has been tested in the rabbit eye. Glyoxal was placed in "grade 5" out of 10 grades. A 15 % dilution of glyoxal in the rabbit eye produced corneal necrosis, but 3 % solution did not (9).

With a modified Magnusson-Kligman test on guinea pigs the sensitising capacity of glyoxal was tested. A 10 % solution of glyoxal was used on 30 animals. Glyoxal was found not to be a potent allergen as 86 % of the animals were sensitised. Cross-sensitization was shown between glyoxal, formaldehyde and glutaraldehyde (13).

Glyoxal solutions (30 % and 5 %) discoloured bits of coverall material and excited skin of normal mice (18).

(In an unpublished study, dermal irritancy was tested in the rabbit. The primary irritation score, calculated on the basis of erythema and edema readings at 24, 48 and 72 hours, was 2.58. Maximum is 4.0.)

10.2 Acute toxicity

The oral LD₅₀ in rats has been reported to be 1.1 g/kg bw or 2.02 g/kg bw. The dermal LD₅₀ was reported to be 6.6 g/kg bw for rabbits when a 20 % solution was tested. The oral LD₅₀ in guinea pigs has been reported to be 0.76 g/kg bw (9, 37, 39). In another report the oral LD₅₀ for rats was given as 7.45 ml/kg bw (5.35-10.4) for a 20 % solution of glyoxal. The dermal penetration LD₅₀ was given as >20 ml/kg (38).

(In an unpublished study, the 4h LC₅₀-value was determined. However, the highest dose used, 1300 mg/l (1.5 mg/l air), did not kill any of the rats. Signs of intoxication were irregular breathing and blood in the nose.) (In another unpublished study, the LC₅₀ for Wistar rats was 245 mg glyoxal/l (2.44 mg glyoxal/l air) and the oral LD₅₀ was given to be 2960 mg/kg bw.)

10.3 Short-term toxicity

A study of subchronic oral toxicity of glyoxal via drinking water in rats has been reported (44). Groups of Sprague-Dawley rats were given glyoxal for 0, 30, 60, or 90 consecutive days. The doses were 0, 2000, 4000 or 6000 mg/litre drinking water. One group received the highest dose for 180 days. The average daily intake of glyoxal was 107-188 mg/kg bw, 234-407 mg/kg bw and 298-451 mg/kg bw, respectively. Body weight gain and organ weights were significantly decreased with dosage. In the high dose group there was a slight papillary change in the kidneys after 90 and 180 days. Serum enzyme (AST, ALT, LDH) and protein levels were significantly reduced at the two highest doses. In liver and
erythrocytes an induction of both glyoxalase I and glyoxalase II was observed after 30 days.
(As presented in an unpublished report, daily administration of glyoxal in drinking water to rats for 28 days at 100, 300 or 1000 mg/kg bw induced a dose-related decrease in water consumption, food consumption and body weight gain at 300 and 1000 mg/kg bw. No microscopic or macroscopic pathological findings were seen that considered to be compound-related.)

10.4 Long-term toxicity and carcinogenicity
In a tumour promoting test, Wistar rats (30 animals/group) were given an initiator or water and thereafter glyoxal or water. The initiator used was N-methyl-N-nitro-N-nitrosoguanidine (MNNG), given for 8 weeks in the drinking water (100 mg/l) together with 10% sodium chloride. Where glyoxal was used it was given in the drinking water (0.5%) for 32 weeks. The animals were killed at week 40 and examined histologically. Glyoxal treatment significantly increased the incidence of adenocarcinomas in the pylorus of the glandular stomach of rats that were pretreated with MNNG and sodium chloride. The results indicate that glyoxal exerts tumour promoting activity on rat glandular stomach carcinogenesis. The mechanisms underlying the promoting effects of glyoxal remain, however, unclear (40).

10.5 Mutagenicity and genotoxicity
In the so-called Ana test in Salmonella typhimurium, strain BA13 (araD332, hisG46, AuvRb, pKM101) glyoxal was mutagenic. The test was carried out in the absence of metabolic activation (1).
Glyoxal was tested in Ames test using strain TA 98 and TA 100 of Salmonella typhimurium with and without S9-mix. A 30% water solution of glyoxal was used. A dose-related effect on the number of revertants in the TA 100 strain was observed. Activity against strain TA 98 was, however, not observed (2). When using the strain TA 102, glyoxal was shown to be mutagenic both with and without S9-mix (23).
In the study of mutagenesis by glyoxal in Salmonella tester strains TA 100 and TA 104 it was suggested that single oxygen formed from glyoxal is related to its mutagenicity. The mutagenesis was independent of intracellular levels of superoxide dismutase and catalase although glyoxal repressed them (42).
The interaction of glyoxal with semiconservative DNA synthesis and with unscheduled DNA synthesis induced by X-rays on TC-SV40 hamster cells has been studied. The evaluation was made by measuring the incorporation of [3H]thymidine into the newly synthesised DNA. The glyoxal concentration used (5 x 10^-5 M) inhibited semiconservative DNA synthesis and potentiated unscheduled DNA synthesis (8).
Glyoxal induced sister-chromatid exchanges in Chinese hamster ovary cells in vitro and in human peripheral lymphocytes in vitro. In hamster ovary cells, but not in human peripheral lymphocytes, glyoxal induced an increase in endoreplicated cells. The increase was reduced when bisulfite was present. Bisulfite reacts with carbonyl groups to form addition products (41).
Glyoxal at doses of 50 - 550 mg/kg bw to male Fischer rats induced DNA damage in the pyloric mucosa of the stomach as detected by a 5- to 12-fold increase in the elution rate constant 2 h after administration. A positive control (the glandular stomach carcinogen N-methyl-N-nitro-N-nitrosoguanidine) induced a similar increase but a negative control (2-acetylaminofluorene) did not increase the elution rate constant. The authors (14) conclude that glyoxal is genotoxic in this region of the gastro-intestinal tract.
The same research group (16) has also studied the potential initiating and promoting activities in the rat (Fischer 344) glandular stomach of glyoxal. The male rats were given doses of 150 to 400 mg/kg bw by gastric intubation. The maximal dose was about half the LD50 value. The highest dose induced up to 100-fold increase in ornithine decarboxylase activity in serum with a maximum after 16 hours. This treatment also induced a more than 10-fold increase in DNA synthesis with a maximum after 16 hours, and, furthermore, glyoxal induced apparent unscheduled DNA synthesis in the pyloric mucosa of the stomach within 3 hours after administration. The results suggest, according to the authors, that glyoxal has potential tumour-promoting activities and may also have initiating activities in the glandular stomach (16).
Glyoxal has been shown to induce DNA-strand breaks in mouse lymphoma cells. The concentrations used were from 1.85 mM to 3.69 mM glyoxal, which were not toxic to the system as measured by viability (17).
Single-strand breaks of DNA were induced after exposure of primary cultured rat hepatocytes to 0.1 - 0.6 mg glyoxal per ml for 60 minutes. Single-strand breaks were also detected in livers of rats (Sprague-Dawley) within 2 hours following a single oral exposure to 200 - 1000 mg/kg bw, with a maximum around 9 hours after administration. The breaks were almost fully repaired 24 hours after exposure (45).
Positive results have been reported when glyoxal was tested in the mouse lymphoma TK". TK" forward mutation assay (65). Glyoxal has also been shown to induce chromosome loss and mitotic recombination in Saccharomyces cerevisiae (49).

10.6 Reproductive and developmental toxicity
In the literature no studies concerning glyoxal and reproductive and developmental toxicity have been found.

10.7 Other studies
The effect of glyoxal on protein synthesis has been studied in vivo. Groups of four Sprague-Dawley rats were given 0 or 150 mg/kg bw intravenously or 0 or 1000 mg/kg bw orally. After 2 hours the animals received intraperitoneally L-[4,5-
H]leucine and after further two hours they were killed and the radioactivity was measured in liver, kidneys and spleen. A great decline in the incorporation of tritiated leucine was shown, particularly in the liver (44).

Glyoxal (0.5 mM) has been shown to be cytotoxic for human fibroblasts in culture, primarily by blocking DNA and protein synthesis. It was assumed that glyoxal inhibits DNA replication and transcription but only in the later phase of action (27).

The effect of glyoxal on the proliferation of E. coli has been studied. The tested concentration of glyoxal, 10⁻³ M, showed a moderate blocking effect on cell division. The cells were gradually recovering from this block. It should be noted that methylglyoxal had an inhibitory effect due to the inhibition of protein synthesis (12).

Glyoxal has been shown to inhibit the respiration of rat brain, kidney and heart slices but not of liver slices. The two enzymes hexokinase and triphosphate dehydrogenase of rat brain and muscle were strongly inhibited by glyoxal at a concentration of 0.7 x 10⁻³ M (29).

11. Observations in Man

11.1 Acute effects by contact and systemic distribution

In a study 65 cases of occupational contact dermatitis from antisepctic components used in hospitals were reported from one French hospital during 1965 to 1990. Patch testing of the patients demonstrated that 41 were sensitized to at least one of the three aldehydes formaldehyde, glutaraldehyde and glyoxal (13).

A report of three women showing a contact allergy which was rapidly induced by contact with glyoxal has been presented. The eczema rapidly disappeared when the contact with glyoxal ceased (5).

Nine out of 14 workers who had contact with glyoxal (40% solution) had dermatitis. Locations were face, neck, thorax-abdomen, upper-arm, forearm, hand-finger, thigh and dorsa of feet. Patch test using 20% glyoxal solution showed positive reaction in 7 of the 9 workers (21).

Patch testing with glyoxal on a patient with dry eczema of both hands was negative for a 0.1 % glyoxal solution. With 1% and 10% solutions the results were positive. In this case skin damage from fibre glass spicules may have been a contributory factor to the development of contact sensitivity to glyoxal. The authors (20) conclude that 10% glyoxal appears to be an adequate concentration for patch testing.

In a human maximisation test for contact allergens glyoxal was given grade 5 (scale 1 to 5) for sensitization. The induction concentration was 10% and the challenge concentration 2.0%. Glyoxal is thus a strong human contact sensitizer (28).

The low-molecular-weight aldehydes and the unsaturated aldehydes are particularly irritating. The mucous membranes of the nasal and oral passages as well as the upper respiratory tract are affected, producing a burning sensation, an increased ventilation rate, bronchial constriction, choking and coughing (3). It has, however, been stated that glyoxal vapours do not irritate the skin or mucous membranes, and the liquid does not burn the skin, although it may discolor it. No exposure levels are given (19).

11.2 Effects of repeated exposure on organ systems

Glyoxal has been found to induce "tanning" of the skin. In a study five patients were repeatedly painted (5 to 7 times) with 30% and 5% glyoxal solutions. Three severe vesicular and hemorrhagic reactions were noted. In one individual focal eczematous responses were elicited in previously painted sites (18).

There are no epidemiological studies reported in the literature on effects of repeated exposure of glyoxal on man.

11.3 Genotoxic effects

No data have been found in the literature.

11.4 Carcinogenic effects

There are no data in the literature on carcinogenic effects on human by glyoxal.

11.5 Reproductive and developmental effects

No data on reproductive and developmental effects have been found in the literature.

12. Dose-Effect and Dose-Response Relationships

12.1 Single / short-term exposures

There are no data on effects by airborne glyoxal on humans. Water solutions of glyoxal have been described as a strong skin sensitizer in humans.

Most animal data refer to oral administration of glyoxal. The oral LD₅₀ in rats is about 2 g/kg bw and in guinea pigs 0.75 g/kg bw. A daily dose of about 200 mg/kg bw for 90 days seems to be the lowest observed effect level (LOEL) in rats after oral dosing. At this dose level a decreased body weight gain was seen as were reduced levels of serum enzymes and proteins. Gastric intubation of 550 mg glyoxal per kg body weight gave a significant increase in the elution rate of
DNA from the pyloric mucosa in rats, indicating genotoxic action. At 50 mg/kg bw there was a slight increase.

Although there are no human data, glyoxal should be treated as an irritating agent. It may, as other low-molecular-weight aldehydes, affect the skin, the mucous membranes and the eyes. It is probably less irritative than formaldehyde.

12.2 Long-term exposures

There is only one animal study where glyoxal has been given for more than 3 months. In this study rats were initiated by N-methyl-N-nitro-N-nitrosoguanidine whereas they received glyoxal for 32 weeks. The purpose of the study was to find out if glyoxal exerted a promoting activity on rat glandular stomach carcinogenesis. At least for this type of carcinogenesis glyoxal seems to act as a promoter.

13. Previous Evaluations by (Inter)National Bodies

Glyoxal has not been evaluated previously by WHO (IPCS or IARC), the German MAK-committee, US NIOSH, the ACGIH, nor by any other national or international body as far as can be judged from the literature.

14. Evaluation of Human Health Risk

14.1 Groups at extra risk

Individuals sensitised to formaldehyde or glutaraldehyde seem to have a greater risk for reacting to glyoxal. There seems to be a possibility for cross-reactions, between these aldehydes. Glyoxal as such is, however, said to be a strong human sensitizer.

14.2 Assessment of health risks

Data from occupational exposure to glyoxal are scarce. Direct skin contact with glyoxal should, however, be avoided. Also water solutions of glyoxal can irritate and affect the skin. There is also the risk of being sensitized.

From animal studies there are indications that glyoxal has a tumour promoting effect in the glandular stomach of rats. A risk for human stomach cancer can not be ruled out, although the risk must be considered to be very small after inhalation exposure due to the reactivity of glyoxal. On the other hand mutagenic effects of glyoxal might be induced in cells in the nose and upper airways absorbing glyoxal from the surrounding air.

14.3 Scientific basis for an occupational exposure limit

There are very few data which can be used as a scientific basis for an occupational exposure limit for glyoxal. There are no data from inhalation exposure. The critical effect based on these few data, is irritation of the skin and the mucous membranes. Moreover, glyoxal is a skin allergen and it has mutagenic properties, which might be a critical effect. Glyoxal might act as a promoter in the carcinogenic events.

15. Research Needs

There is a need for measurements of glyoxal in the workroom air. Investigations concerning reactions between glyoxal and other components in the workroom air are desirable. Also toxicokinetic data are missing. In order to evaluate the risk of exposure to glyoxal in the work environment data on uptake, distribution, biotransformation and excretion are desirable. The local effect in the nasal mucosa should be compared to the effects of e.g. formaldehyde. There is a lack of inhalation studies for the evaluation of mutagenicity and carcinogenicity. Also, the carcinogenic properties of glyoxal from a mechanistic point of view should be further investigated.
18. References

Data Bases Used in Search for Literature

In the search for literature the following data bases were used:
- NIOSHTIC
- Cancerline
- Chemical Abstracts
- Medline
- Toxline

The search was performed January 23, 1994, at the library of the Swedish National Institute of Occupational Health. In order not to miss any references the only search-words used were "107-22-2" (the CAS nr) and "glyoxal".

Submitted for publication January 24, 1995.
Appendix 1

Permitted or recommended maximum levels of glyoxal in air

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* - an occupational exposure limit is not available

References