FORMALDEHYDE: USES, TOXICOLOGY, ANALYSIS, TREATMENT AND UNDERLYING MECHANISMS

A M.Sc Dissertation Report by:

Sweta S. Harmalkar

SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403 206

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FORMALDEHYDE: USES, TOXICOLOGY, ANALYSIS, TREATMENT AND UNDERLYING MECHANISMS

A DISSERTATION REPORT (literature review)

Submitted in partial fulfilment of

The degree of M.Sc. (Biochemistry)

BY

Ms. Sweta Suresh Harmalkar

To the

School of Chemical Sciences

Goa University

Goa 403206

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DECLARATION

I declare that the literature review titled, "**FORMALDEHYDE: USES, TOXICOLOGY, ANALYSIS, TREATMENT AND UNDERLYING MECHANISMS**" has been carried out by me as a part of my M.Sc. Biochemistry program in the Chemistry department, School of Chemical Sciences, Goa University. All the information (text, figures) derived from the literature review has been duly acknowledged in the text and a list of references is provided.

Sweta Harmalkar:

Signature:

Date:

CERTIFICATE

This is to certify that the literature review entitled, ”Formaldehyde: Uses, toxicology, analysis, treatment and underlying mechanisms” submitted by the student is the record of research work carried out by the candidate during the academic year 2021-22 under my supervision in partial fulfilment of the requirements for the degree of Master of Science in Biochemistry.

Dr Roshan R. Naik
(Project Guide)

Prof. Vidhyadatta M. Shet Verenkar
(Dean of SCS, Goa University)

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Abstract

Formaldehyde is a natural disinfectant and embalming agent. Due to its tendency to convert into a variety of chemical derivatives, it has found its place as one of the most widely used industrial chemical. At the same time it is extremely toxic even at very small concentrations. Its single most common use, is a raw material in the manufacturing of resin or glue used as a permanent adhesive and wood products. Millions of people work in formaldehyde based industries across the world.

The wastewater effluent of these industries contains low to high concentration of formaldehyde, which, if discharged untreated, poses a great danger to environment and human life. The objective of this literature review is to study various uses and laboratory methods for determining formaldehyde concentration in wastewater and also to study method of treatment of formaldehyde based on industrial waste water.

keywords: Formaldehyde, Waste water treatment, Toxicity, Environmental concern, Harmful effects, kinetics

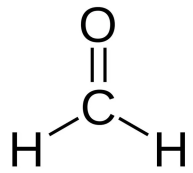
1. INTRODUCTION

Water shortage is one of the major environmental problems that world is currently facing and require more attention to tackle before discharging wastewater into rivers, lakes and other water bodies. This waste-water must be initially treated since it contains organic materials and harmful heavy metals which could affect the human health and the environment especially to the aquatic lives. Formaldehyde (CH_2O) is a most widely used chemical. It is commonly in the production of polymers such as formaldehyde resins, phenolic resins and melamine resins. As resins, its used in permanent adhesives such as surface coating, foams and insulation, fireboard, plywood and carpeting. It is a widely used chemical in hospital industry as a preservative and fixative especially in medical laboratories. Formaldehyde is hazardous to living beings because it inhibits cell physiological action by forming persistent bonds with protein amino groups. In bacteria and mammalian cells, formaldehyde induces DNA damage and mutations, and hence poses a carcinogenic risk.

The International Agency for Research on Cancer (IARC) has classified formaldehyde as group 1 carcinogenic substance. Thus effluents containing formaldehyde must be treated to prevent cancer risk in humans and preserve aquatic ecosystems.

1.1 Structure of formaldehyde:

It is a simple chemical compound made up of hydrogen, oxygen and carbon.



Formula: CH_2O

IUPAC ID: Methanal

Molar mass: 30.031gm/mol
Density: 815kg/m^3
Boiling point: -19^{0}c
Classification: Aldehyde, organic compound.
Molecular geometry: Trigonal planer.
Hybridization: Sp^2
Levels: 0.02—4ppm (indoor air level)
: 0.0002 to 0.006ppm (outdoor air level in rural areas)
: 0.001 to 0.02ppm (outdoor air level in urban areas)

1.2 OCCURRENCE OF FORMALDEHYDE

- It is a gaseous pollutant.
- Outdoor sources of occurrence includes power plants, manufacturing facilities, incinerators and automobile exhaust emissions. Other sources include forest fires and other natural sources.
- Indoor sources include release of formaldehyde from various building materials, consumer products and tobacco smoke, etc.

- Natural occurrence: It is naturally formed in the troposphere layer of the atmosphere during the oxidation of hydrocarbons after reacting with hydroxyl radicals and ozone.
- Terpenes and isoprene produced by foliage react with hydroxyl radicals in the vicinity of vegetation to create formaldehyde as an intermediate product.They usually have a short half life.
- It is also formed by decomposition of plant residues in the soil and hence is present in some fruits and vegetables.

1.3 FORMALDEHYDE IN AN OCCUPATIONAL SETTING

The sources of exposure to formaldehyde includes:

- For example, formalin is commonly utilised in the chemical industry for resin synthesis.
- As a fixative and disinfectant, it is used as a preservative in medical laboratories and hospitals.
- It is present as a residue and is released from formaldehyde-based resins and through their decomposition through heat e.g. in the production of wood, textiles, synthetic vitreous insulating materials, and plastics When compared to urea, it has the advantage of releasing less formaldehyde and other melamine based resins.
- It is also a product of pyrolysis or the combustion of organic matter e.g. fire fighting.

1.4 USES OF FORMALDEHYDE

- It is used in production of many personal care and consumer items wherein these products contain formaldehyde and it is released slowly over a period of time to act as a preservative and destroy the harmful microorganisms, prevent bacterial and pathogenic growth, eventually increasing the products shelf life.
- It is used in the production of formaldehyde resins which are later used to make interior moulded components to withstand at high temperatures such as flooring material, household furnishings, cabinetry and some types of wood panels.
- Formaldehyde resins are used to produce highly durable exterior primers, brake pads and fuel system components in automobiles.

- Formaldehyde is used by various industries in the formation of photographic film, decorative laminates, plywood panelling, and plastic parts.
- In glues that connect particleboard together, urea-formaldehyde is utilised.
- It is also used as a disinfectant in hospital settings and for preservation of biological specimens in mortuaries, and veterinary clinics.
- In gel electrophoresis of RNA, formaldehyde is used as a denaturing agent so that the secondary structures are not formed.
- Formaldehyde is used :
    1. In cosmetic industry for preservation of soaps, deodorants, shampoos, addictive in nail hardeners, hand creams etc.
    2. In the food industry for the preservation of dry goods, container disinfection, seafood preservation, and certain types of oils and fats.
    3. In metal industry: anticorrosive agent and electroplating processes.
    4. In Photographic industry: for developing accelerator and hardener for gelatine layers.
    5. In sugar industry: as infection inhibitor in producing juices.
    6. In wood industry it is used as a preservative.

1.5 ENVIRONMENTAL CONCERN RELATED TO FORMALDEHYDE

Since formaldehyde is a very highly reactive, water soluble and rapidly metabolized, on contact with skin it causes irritation and skin sensitivity reactions at the site of contact with formaldehyde or formalin containing compounds. Formaldehyde is used for various means for e.g. preservative used in hospital industry is released into the environment through various water streams. Formaldehyde is also used in the form of fertilizer and is released directly in the environment causing ecological hazards. Major sources of environmental exposure includes the combustion processes mainly due to the auto emissions and photo oxidation of hydrocarbons from automobiles. Another source of exposure is that, it is used as a fumigant and sterilant and is used as an embalming fluid in anatomy labs, morgues etc. cigarette smoking is another means of formaldehyde with human exposure. Exposure to formaldehyde occurs in occupational settings during the manufacture, processing and handling of formaldehyde and its by-products via inhalation and dermal (skin) route.

1.6 TOXIC KINETICS OF FORMALDEHYDE

- It is essential metabolic intermediate in all cells and is found during metabolism of xenobiotic and amino acids.
- Half-life of formaldehyde in blood is about 1.5 minutes and hence it is rapidly metabolized.
- Formaldehyde is metabolized to formate by enzyme formaldehyde dehydrogenase associated with glutathione.
- Tetrahydrofolate-dependent one-carbon biosynthetic pathways also result in oxidation to carbon dioxide or incorporation into thymidine, purines, and amino acids.
- Formaldehyde can cross link proteins and single stranded DNA.
- Exogenous formaldehyde is readily absorbed from the respiratory tract and gastrointestinal tract.
- Little to no formaldehyde is excreted unmetabolized.

2.0 MECHANISM OF FORMALDEHYDE TOXICITY

The exact mechanism of action is not clear. it is found to interact with cell membrane

and the other bodily tissues interrupting the cellular functions.

Formaldehyde's electrophilic location, the carbonyl atom, allows it to easily react with nucleophilic sites on cell membranes, in body fluids and tissues, such as amino groups in protein and DNA. Protein precipitates with higher formaldehyde concentrations.

When intracellular levels of formaldehyde rise to the point where formaldehyde dehydrogenase activity is saturated, the unmetabolized whole molecule can exercise its effects locally.

Formaldehyde is a very strong crosslinking agent even in the low concentration range. The reaction mechanism of this agent is the initial addition of formaldehyde to a primary amine on either an amino acid residue or DNA base to yield a hydroxymethyl intermediate. Then the hydroxymethyl group condenses with a second primary amine to yield a methylene bridge.

Formaldehyde is oxidised to formate by mitochondrial aldehyde dehydrogenase or via two enzyme system which converts non enzymatically formed glutathione adducts (S-hydroxymethylglutathione) to the intermediate S-formylglutathione, which is then metabolized to formate and glutathione by S-formylglutathione hydrolase.

Formaldehyde therefore causes the proteins to precipitate which further causes coagulation necrosis of the exposed tissue. Post inhalation injury, it causes local irritation of the upper respiratory tract and in severe cases might also lead to spasm and laryngeal oedema and anaphylaxis.

Gastrointestinal exposure to formaldehyde also causes adverse reactions. Formaldehyde undergoes delayed absorption but once absorbed, it is metabolized to formic acid, which is responsible for causing acid-base imbalances in the body and other systemic effects on the body.

Formaldehyde has a half-life of roughly 1-15 minutes in plasma before being transformed to carbon dioxide and expelled from the lungs. The amount of formate salts and other metabolites discharged in the urine is lower.

2.1 Acute and Short-Term Toxicity in humans

Formaldehyde is genotoxic, mutagenic, teratogenic, embryo toxic and carcinogenic chemical and has tendency to cause gene mutations, chromosomal errors, single chain fractures and cellular modifications.

Based on ingestion of a 37 percent solution, the median fatal dose for formaldehyde has been calculated to be around 523 mg kg-1. Irritation and burning of the mucous membranes of the mouth, nose, and upper respiratory tract are the most common side effects of acute formaldehyde inhalation exposure.

Inhalation (acute) Weakness, nausea, vomiting, pneumonia, headache, dyspnea, coughing, wheezing, laryngeal and pulmonary edoema, laryngeal spasm, bronchospasm, respiratory depression, obstructive tracheobronchitis, central nervous system depression, convulsions, and coma are all possible side effects of formaldehyde exposure.

Significant amounts of formaldehyde inhaled as a result of the start of pulmonary edoema or respiratory collapse can be lethal. Abrupt intake of formaldehyde causes

mouth irritation, throat burns, and gastrointestinal ulceration, as well as chest or abdominal pain, nausea, vomiting, diarrhoea, and gastrointestinal haemorrhage, metabolic acidosis, tachypnea, jaundice, proteinuria, hematuria, and acute renal failure.

After oral ingestion, formaldehyde produces a local corrosive effect in the upper gastrointestinal system. Necrosis, Perforation and bleeding along with nausea, diarrhoea and abdominal pain.

Exposure to gaseous formaldehyde or splashes of formaldehyde-containing liquids is corrosive and can cause skin irritation, burns, and eye irritation, which can lead to irreversible vision changes or blindness.

2.2 Chronic Toxicity in Animals/ Humans

Inhalation exposure of formaldehyde at concentrations up to 15 ppm for 6 weeks in rats has been investigated. At doses >6 ppm a dose-dependent increase in lesions of the nasal passages and significant increase in cell proliferation in the nasal cavity was reported. Furthermore, reduction in body weight, laboured breathing, listlessness, and hunched posture have been reported in mice administered up to 40 ppm of formaldehyde for 13 weeks.

2.3 Immunotoxicity

Formaldehyde is a sensitising agent that can trigger an immunological response when exposed for the first time. According to certain animal research, formaldehyde may increase their sensitivity to breathed allergens. Immunotoxic effects of formaldehyde exposure include altered cellular immunity, including T lymphocytes, B lymphocytes, and NK cells that produce incorrect cytokines. A healthy immune system recognises and destroys harmful tumour cells in the normal course of things, but impaired immune function, combined with DNA damage, increases the risk of cancer.

2.4 Reproductive Toxicity

At dosages below those causing severe maternal toxicity, studies of formaldehyde's reproductive and developmental toxicity in mice, rats, rabbits, and dogs following

ingestion, inhalation, or skin exposure have found no fetotoxic, embryotoxic, or teratogenic effects. There is no evidence that formaldehyde alters the shape of sperm or causes spontaneous miscarriages in humans. As a result, formaldehyde is not regarded as a reproductive or developmental hazard.

2.5 Genotoxicity

An increase in sister chromatid exchanges in cultured human lymphocytes treated with formaldehyde showed positive results for unscheduled DNA synthesis and chromosomal aberrations in the absence of metabolic activation have been reported. *In vivo* studies in rats and monkeys exposed to formaldehyde by inhalation have reported positive results for DNA-protein cross-links in the nasal mucosa and positive results for chromosomal aberrations. In vitro and in vivo, formaldehyde has a high direct acting mutagenesis potential; consequently, it is considered mutagenic at the point of contact.. There is less evidence to show that formaldehyde may be genotoxic in humans. Increases in DNA-protein cross-links, as well as significant increases in chromosomal abnormalities and chromosomal breakdown, were found in studies of workers exposed to formaldehyde on the job.

2.6 Carcinogenicity

The National Cancer Institute (NIC), which is part of the National Institute of Health (NIH), has concluded that there is sufficient evidence for formaldehyde's carcinogenicity in humans following occupational exposure. Based on number of cohort studies conducted by International agency for Research on Cancer, formaldehyde may cause malignancies such as lymphoma, leukemia, and testicular interstitial-cell adenomas especially in anatomists and embalmers. Sufficient evidence showed that formaldehyde causes nasopharyngeal cancer, sinonasal cancer, and leukemia in human particularly myeloid leukemia.

3.0 CLINICAL MANAGEMENT OF EXPOSURE

Management of Dermal/ Ocular/ Inhalation injury:

- Symptomatic and supportive management.
- Removal of the inhaled contents is the first treatment.

- Oxygen therapy and use of bronchodilators can be administered. Incase of upper airway oedema, altered mental status or coma the patient may be given a mechanical ventilator support and endotracheal intubation.
- Decontamination of the exposed area and clothing by washing the area with soap and water and rinsing of eyes with water or saline.
- There is NO antidote for formaldehyde toxicity. In case of severe cases, formaldehyde and formic acid can be efficiently removed by haemodialysis.
- Folate can be administered to augment elimination of formic acid. In case of ingestion, it can be decontaminated with milk or water followed by bolus of charcoal and a mild saline cathartic is useful.

4.0 ANALYTICAL METHODS FOR DETECTING FORMALDEHYDE

There are several methods employed in detection of formaldehyde those are: colorometry, Flourimetry, High Performance liquid chromatography(HPLC), Polarography, Gas chromatography and the most common Spectophotometry. Infrared detection and gas detector tubes are also used to monitor workplace atmosphere.

Laboratory tests:

- 3-methyl-2-benzothiazoline hydrazine (MBTH) method: carried out using spectrophotometer and MBTH developing solution, KMno4, NaoH, Chromic acid cleaning solution.
- Hantzsch reaction: test is done using spectrophotometer using Hantzsch reagent acetoacetanilide reagent.
- NIOSH Procedure: it is also done using chromotropic acid and conc.H2SO4 solution.
- Modified NIOSH procedure : Done using spectrophotometer and chromotropic acid reagent and HCL + H202.
- Iodometry: instrument used is spectrophotometer and potassium iodate + potassium iodide + sodium thiosulfate sulfuric acid and sodium hydroxide.

5.0 TREATMENT OR REMOVAL OF FORMALDEHYDE

1. Biological treatment methods:

   By use of Yeast culture and mixed bacterial culture: There are certain types of bacteria resistant to formaldehyde. To prove these hypothesis, a study was conducted using two such bacteria's namely *Pseudomonas putida and Pseudomonas cepacia* and yeast of *Tricosporon generum* namely *Richosporom penicillatum.* the result of the treatment showed 90% reduction and removal of formaldehyde, butanol and methanol in 24hours.

   By use of Activated sludge: for example, from municipal sewage, slaughterhouse waste, food processing industry effluents etc is added with nitrogen and phosphorus salts to cause breakdown of formaldehyde. This process usually needs a special plant for purification and is comparatively slow.

   By use of biomas in a biological reactor using ammonia salts: Biological nutrients like nitrogen and phosphorus are used as feed. It is done by holding the flow of waste water to avoid mixing with ammonia. therefore before the mix, this is transferred in a reactor as two separate streams so that nitrogen is consumed by biomas before coming in contact with formaldehyde. The streams are separated in order to prevent formation of urotropine which is non biodegradable.

2. Chemical methods:

   By Photo-fenton process : The method is used for water containing formaldehyde and methanol. Fentons reagent (solution of hydrogen peroide and iron catalyst) is used to oxidise waste water. Initially in the reaction formaldehyde and methanol are decomposed. later, in second and third stage there is rapid degradation of both chemicals. The initial Ph at 2.6 shows the highest removal efficiency.

   By using ozone, Magnesium oxide and hydrogen peroxide: This is called as catalytic advanced oxidation process of 0_3/MgO/H_20_2. 7.5-8.0 moles of phenol plus another 2 moles of hydrogen peroxide per mole of

formaldehyde present in water. Temperature required for the reaction is 20^{o}C and the time limit is 30-60 minutes to complete.

Treatment by lime solution: formaldehyde reacts with lime to produce non toxic ketoses and aldoses. the treatment is done by adding 2gm/l of lime at 18-20^{o}C for 3-4days or at 60^{o}C for 20-30 minutes. The colour changes are observed accordingly.

Treatment by air oxidation: Also called as liquid phase oxidation. In this the reactor is heated to 200^{o}C. Air is fed through it at 40bar pressure. The rection results in 80-93% reduction in non-oxidised formaldehyde.

Physical treatment methods: physical methods such as distillation are used incase of high concentration of formaldehyde.

6.0 CONCLUSION

It may be observed from the review that formaldehyde is a toxic chemical and one need to be very vigilant while handling it. Its effects are detrimental to health that might vary from mild allergic symptoms to severe anaphylaxis. Utmost care to be taken during the handling process and immediate interventions to be taken post exposure.

There are various methods to detect as well as to remove formaldehyde from waste water. However, unfortunately, there is not a single particular method which can separate formaldehyde completely. Each method used has its own drawbacks or limitations.

It is important to analyse and determine the concentration of formaldehyde prior to treatment.

A combination of chemical treatments followed by biological treatment can be called as the most suitable option so as to achieve maximum positive results.

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