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The Health Risk of Formaldehyde to Human Beings

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Abstract: Problem statement: Formaldehyde was classified as a potential human carcinogen, identified by the US Environmental Protection Agency and International Agency for Research on Cancer as a Class 2A carcinogen. It also can cause irritation to human. However, formaldehyde present in biological fluids or tissues and environment as a result of natural processes or from man-made sources and can be emitted slowly into the air. Formaldehyde was used in many industries, hospitals and research as a sterilizing and preserving agent. The utmost concern of this study was about the present of formaldehyde in seafood product. **Approach:** A review was done on the health effect adverse by formaldehyde, formaldehyde toxicity to human, formaldehyde in seafood and methods to control formaldehyde in food and seafood. Google, Pubmed, Science Direct and Scopus were used in preparation of this review. **Results:** This review clarified that one of the formaldehyde source to human was seafood. Previous study showed that seafood contained high amount of formaldehyde because of natural production by postmortem enzymatic reaction besides the used of formaldehyde as preservative. Based on prior studies, exposure to formaldehyde can cause irritation and genotoxicity effect. For cancer effect studies, formaldehyde was long considered as a potential human carcinogen based on experimental animal studies and limited evidence of human carcinogenicity. **Conclusion:** Several mefinding of many health effect of formaldehyde, suggests that the investigation of level of formaldehyde in seafthods have been suggested to reduce formaldehyde in food such as cooking and washing. The ood should be done and also the level of formaldehyde natural production.

Key words: Formaldehyde, fish, natural formaldehyde, leukemia, formaldehyde genotoxicity, formaldehyde toxicity, cancer

INTRODUCTION

Recent trends in global food production, processing, distribution and preparation are creating an increasing demand for food safety research in order to ensure a safer global food supply[1]. However, chemical contamination in food results in the major sources of the foodborne disease[2,3]. Among them, great attention has been paid toward volatiles toxic aldehydes like formaldehyde, which has been reported by the International Agency for Research on cancer[4] as carcinogenic to humans[5-8].

Formaldehyde is present in biological fluids or tissues and environment as a result of natural processes or from man-made sources. Formaldehyde is biologically present in many interior construction materials of houses and can be emitted slowly into the air. Formaldehyde is also used in hospitals, research and teaching laboratories as a sterilizing and preserving agent. Formaldehyde is a highly reactive agent which can react with macromolecules in biological systems[9,10].

Most commercial formaldehyde is produced from methanol. Formaldehyde is widely used and important in the chemical industry as a solvent and raw material for the production of phenolic polymers which are synthesized by the condensation of phenol and formaldehyde[11].

Formaldehyde used predominantly in the synthesis of resins, with urea-formaldehyde[12] resins, phenolic-formaldehyde resins, pentaerythritol and other resin[13,14]. Formaldehyde uses also related to fertilizers production and formaldehyde also used for various other purposes, such as preservatives and disinfectant. It also can be used in many industrial processes, including wood fixatives, dry cleaning solutions, solvent use, boiler use, chemical production, oil, gas and petroleum production, as well as paper and pulp production, cosmetics[15], food and the textile industry[10,16].

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For decades, formaldehyde has been applied in many industries and consumer goods with the primary function of ceasing spoilage by microbial contamination. The anti microbial property of formaldehyde has gain place in producing cosmetics, shampoos, sun-ton lotion, shaving creams and many others[15]. It is also used as household cleaning agents and car shampoo[10]. The use of formaldehyde in medical field is relatively small, primarily as antiseptic and fumigant[17].

In the agriculture industry, formaldehyde has been used as fumigant, as a preventative for the mildew and spelt in wheat and for rot in oats. It has also been used as germicide and fungicide for plants and vegetables and as insecticide for destroying flies and other insects[10].

With much attention, the utmost concern of this study is about food industry. In food industry, formaldehyde is used as an antibacterial agent and preservative in processing of foodstuffs[10]. It widely used in food processing for its bleaching effect and also as preservative in order to prevent the product from spoilage by microbial contamination[18]. Formaldehyde was used as a preservative in dried foods, fish and certain oils and fats, disinfections for containers as well as modifying starch for cold swelling. It is sometimes added inappropriately in food processing for its preserving and bleaching effects such as dried foods, vermicelli, tripe and chicken paws[18]. It is also found in cheese as bacteriostatic agent[4]. In the sugar industry, it is added while producing juices as infection inhibitor[19,20].

Now days, the safety and quality of seafood has arose much public attention. Before putting on shelf, seafood is firstly dipped in formaldehyde-water solution for a period of time by dishonest mongers, in order to prevent from spoiling and to increase the storage time[20] The seafood dipped with formaldehyde is a big danger to the physical health of consumer[21]. Besides, it also used as such as herring and caviar[10]. Due to this issue, voices have to protest to the practice of such chemical in foods[20]. Even though chemical treatment is helpful in controlling spoilage on fish, these chemicals brought about the negative adverse effects upon human consumption, yet such issue is still under controversy.

Since formaldehyde can cause adverse effect to human health, they are prohibited under the Food regulation 1985. Although regulation has been enforced but still there are reports that revealed the practice of such prohibited chemicals in food. Formaldehyde is classified as a mutagen and possible human carcinogen being proved by experiments on microorganisms (mutagenic effect), mice and rats (induction of cancer)[20]. Recently, formaldehyde has been described as one of the chemical mediators of apoptosis.

The purpose of this review is to focus on formaldehyde contamination in the seafood. It also provides an up-to-date critical review of the information for formaldehyde, especially about the existence of formaldehyde in seafood whether as an additive or naturally produces. Besides, this review highlights about the toxicology of formaldehyde and health impact of formaldehyde to human.

The characteristics of formaldehyde: Formaldehyde (CH2O) is also known as methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane and formic aldehyde. Its Chemical Abstracts Service (CAS) registry number is 50-00-0[10]. The physical and chemical properties of formaldehyde was shown in Table 1.

At room temperature, formaldehyde is a colorless gas with a pungent, irritating odor[15]. It is highly reactive, readily undergoes polymerization, is highly flammable and can form explosive mixtures in air[6,8,18]. It decomposes at temperatures above 150°C. Formaldehyde is readily soluble in water, alcohols and other polar solvents. In aqueous solutions, formaldehyde hydrates and polymerizes and can exist as methylene glycol, polyoxymethylene and hemiformals. Solutions with high concentrations (>30%) of formaldehyde become turbid as the polymer precipitates. As a reactive aldehyde, formaldehyde can undergo a number of self-association reactions and it can associate with water to form a variety of chemical species with properties different from those of the pure monomolecular substance. These associations tend to be most prevalent at high concentrations of formaldehyde; hence, data on properties at high concentrations are not relevant to dilute conditions[10].

The most common commercially available form is a 30-50% aqueous solution. Formaldehyde is the most widespread carbonyl compound. It is widely used in consumer goods to protect the products from spoilage by microbial contamination. Formaldehyde is often added to keep food pleasing to the consumers, but this chemical poses a threat to human health[18].

Table 1: Physical and chemical properties of formaldehyde[10]

Property	Range of reported values
Relative molecular mass (Dalton)	30.03
Melting point (°C)	-118 to -92
Boiling point (°C, at 101.3 kPa)	-21 to -19
Vapour pressure (calculated) (Pa, at25°C)	516 000
Water solubility (mg L^{-1}, at 25°C)	400 000-550 000
Henry's law constant (Pa. m^3 moL^{-1}, at 25°C)	2.2×10^{-2}-3.4×10^{-2}
Log octanol/water partitioncoefficient (log K_{ow})	-0.75 to 0.35
Log organic carbon/water partition coefficient (log K_{oc})	0.70-1.57
Conversion factor	1 ppm = 1.2 mg m^{-3}

The toxicity of formaldehyde to man and animals has been reported. The International Agency for Research on Cancer has concluded that formaldehyde is a potential carcinogen for animals and an evidence for the carcinogenicity of formaldehyde inhuman beings has been reported[18].

Toxicity of formaldehyde to human: Formaldehyde concentrations in humans prior to exposure to external source of formaldehyde have been found to be approximately 2 µg g^{-1} of venous blood[22]. Formaldehyde is an essential metabolic intermediate in mammalian cells that is produced during the normal metabolism of amino acids such as serine, glycine, methionine and choline.

Most inhaled formaldehyde is deposited and absorbed in the upper respiratory tract, with which the substance first comes into contact[22]. In humans, due to oral and nasal breathing, depositions and absorption occur in the nasal passages, oral cavity, trachea and bronchus[23].

Formaldehyde is rapidly metabolized to hydroxymethylglutation by formaldehyde-glutathione conjugate. Hydroxymethylglutation is subsequently metabolized to format by formaldehyde dehydrogenase; it is a major metabolic enzyme involved in the metabolism of formaldehyde. Formaldehyde dehydrogenase is widely distributed in mammalian tissues such as liver and red blood cells in humans. After the oxidation of formaldehyde to format, the carbon atom is further oxidized to carbon dioxide or incorporated into purines, thymidine and amino acids via tetrahydrofolate-dependent one-carbon biosynthetic pathways. If formaldehyde is not metabolized by formaldehyde dehydrogenese, it can form cross-linkages between proteins and between proteins and single- stranded DNA. Endogenous or exogenous formaldehyde enters the formaldehyde dehydrogenese metabolic pathway and is eliminated from the body as format in urine or CO2 in expired air[24].

Due to its deposition principally in the respiratory tract and to rapid metabolism, exposure to high atmospheric concentrations of formaldehyde does not result in an increase in blood concentrations in humans[22].

The US Environmental Protection Agency (EPA) has established a maximum daily dose reference (RfD) of 0.2 mg kg^{-1} body weight per day for formaldehyde. At exposures increasingly greater than the RfD, the potential for adverse health effects increases[18].

Formaldehyde in seafood: Fishery products are of great importance for global human nutrition[25]. However, a number of biological, chemical and physical hazards are reported associated with seafood contamination[26]. Microbiological and chemical hazards result in the most significant sources of foodborne diseases. Chemical contamination in food can include natural toxicants, such as mycotoxins[27-29] and marine toxins[30]; environmental contaminants, such as mercury and lead[12,31-35] and naturally occurring substances. Among them, great attention has been paid toward volatile toxic aldehydes like formaldehyde. The WHO reported that highest concentration of formaldehyde was found in marine fish[10]. Besides, Bianchi *et al.*[5] studied that during storage, fish belonging to the Gadidae family have high formaldehyde concentration (from 6.4±1.2-293±26 mg kg^{-1}), in four cases out of 14 exceeding the value of 60 mg kg^{-1} proposed by the Italian Ministry of Health. More over, there is also variable formaldehyde levels were observed among four species squid, which was generally far higher in viscera than in muscle of frozen squid[7]. Table 2 showed the formaldehyde content in some seafood from previous study.

Formaldehyde as seafood preservative and additive: Formalin is a generic term which describes a solution of 37% formaldehyde gas dissolved in water. Formalin was used to preserve fish and other seafood from pathogens due to its anti microbial agent property. Formalin or formaldehyde will be added as a preservative after the fish were caught, during transportation or in storage. This compound also helps to maintain the freshness of seafood because it will react with protein and subsequently causes muscle toughness[5,37].

In the other hand, formaldehyde has been used as food additive in processed seafood such as herring and caviar in some countries[10]. Mutsuga *et al.*[38] studied that Polyethylene Terephthalate (PET) is frequently used as a packaging material for beverage bottles, fruit and vegetable trays, fish and seafood product and egg crates in Japan contain low levels of formaldehyde. Even though the level is low, but it will give negative effect after long term exposure.

Table 2: Formaldehyde content in some seafood

Species	Body region/ part eaten	Formaldehyde Concentration (mg kg^{-1})	Country/ region	Reference
Cod	Flesh	10.38±0.82	Italy	[5]
Dosidicus gigas	Muscle	17.30±1.62	China	[7]
	Viscus	165.0±15.2		
Japanese Ocean	Muscle	10.70±0.16	China	[7]
	Viscus	42.20±1.52		
Ilex argentinus	Muscle	19.70±0.58	China	[7]
	Viscus	412.0±59.6		
Gadus callarias	Flesh	3.300±0.6	Poland	[36]

Besides, formalin is used as a bath treatment to control external parasitic infections of fish. Formalin effectively kills parasites on gills, skin and fins. It is extremely effective against most protozoans, as well as some of the larger parasites such as monogenetic trematodes. Formalin also was employed as aquatic fungi controller in hatcheries and culture facilities. Aquatic fungi (*Saprolegniaceae*) often cause disease problems for fish culturists[39,40]. In addition, high concentrations of formalin are used to control fungi on fish eggs. Since formalin is approved in US and Canada as aquatic chemotherapeutant[39], formalin remains fungicide of choice at fish hatcheries[40]. Formaldehyde is registered as feed under Canada Feed Act. However, formalin usage for aquaculture was not approved in Australia, Europe and Japan due to its association with oncogenesis[41].

Natural production and mechanism of formaldehyde: Formaldehyde develops postmortem in marine fish and crustaceans, from the enzymatic reduction of Trimethylamine-Oxide (TMAO) to equimolar amounts of formaldehyde and Dimethylamine (DMA) as shown in Fig. 1[37]. Different amount of formaldehyde has been observed among the species as well as between fresh and frozen seafood. This condition can be explained by the different level of TMAO from species to species and also enzymatic reaction to reduce TMAO to formaldehyde and DMA that obtained in frozen seafood. A different result was observed in fresh seafood because the reduction of TMAO depend to the bacterial activity[5].

Formaldehyde may be formed during the ageing and deterioration of fish flesh, high level do not accumulate in the fish tissue, due to subsequent conversion of the formaldehyde formed to other chemical compounds. However, formaldehyde accumulated during the frozen storage of some species of fish, including cod, Pollack and haddock[37]. The amounts of formaldehyde formed depend mainly on the time and temperature of frozen storage and it causes muscle toughening and water loss in fish species, leading to lower acceptability as well as functionality[7].

It was reviewed that proteins of fish muscle undergo chemical and physical changes during frozen storage which may result in, under certain conditions (i.e., long periods of storage, poor freezing practices, temperature fluctuations), loss of quality, reflected mainly by an unacceptable texture as well as an undesirable flavor, odor and color[37]. In frozen gadoid fish species, most of these changes are caused by the production of formaldehyde in the muscle.

$$\text{TMAO} \xrightarrow{\text{TMOase}} \text{formaldehyde} + \text{DMA}$$

Fig. 1: Enzymatic reaction of TMOase

It was suggested that the accumulation of formaldehyde and the resulting deterioration of seafood products during frozen storage are primarily caused by the enzymatic activity of trimethylamine oxide aldolase (TMAOase). A screening of muscle samples from 24 species showed TMAOase activity in only the nine gadiform species that were analyzed. Enzyme activities in the major white muscle of gadiform fish showed large variations between species as well as between individuals. A frozen storage experiment showed a similarly large variation in the rate of formaldehyde accumulation, which could be accounted for by the endogenous white muscle *in situ* TMAOase activity. This TMAOase activity also correlated with the rate of insolubilization of otherwise high ionic strength soluble protein. A simple model describing the accumulation of free formaldehyde during frozen storage of gadiform fish is proposed. The model is based on a storage time-dependent decay of substrate-saturated white muscle TMAOase activity[42].

Moreover, the observation showed that formaldehyde content of crab samples increased throughout the storage. Slightly higher formaldehyde content was found in soft shell crab muscle, compared with hard shell counterpart. Claw muscle generally contained a greater amount of formaldehyde than lump counterpart[43].

Health effect to human: Human studies have shown that chronic inhalation exposure to formaldehyde is associated with respiratory symptoms and eye, nose and throat irritation[14,44]. On the other hand, the oral exposure to formaldehyde related to the induction of gastrointestinal tract ulcer. There are also cases of systemic or localized allergic reaction attributed to the formaldehyde have been reported in clothing and textiles[16], bank note paper, medical treatment and household and personal care[10,24].

In clinical studies, eye, nose and throat irritation was experienced in volunteers that exposed to formaldehyde ranging from 0.25-3.0 ppm, eye, nose and throat irritation was experienced[45,46]. Mucociliary clearance in the nasal cavity has been found to be reduced following exposure to 0.25 ppm formaldehyde in volunteers. In healthy volunteers as well as asthma patients, there was no clinical effect on lung function after exposure to formaldehyde up to 3.0ppm for up to 3 h[24,47].

In genotoxicity studies, formaldehyde is considered to be a weak genetic toxicant at the first contact[24]. Studies of genetic effects in buccal or nasal mucosal cells[48,49] and in lymphocytes pheripheral[50] have been observed in individuals occupationally exposed to formaldehyde but in some studies, genetic effects of formaldehyde were not observed in lymphocytes pheripheral[24].

Besides, an increased incidence of micronucleated buccal or nasal mucosal cells has been reported in some surveys of individuals occupationally exposed to formaldehyde[48,49]. Evidence of genetic effects like chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes from individuals exposed to formaldehyde vapor has also been reported in some studies[10,51]..

Moreover, formaldehyde is genotoxic *in vitro* in cultured mammalian cells. When formaldehyde reaches the nuclear DNA, it forms DNA-protein cross-links (DPX). Incomplete repair of DPX can lead to the formation of mutations, in particular chromosome mutations and micronuclei (MN) in proliferating cells. Due to its high reactivity, formaldehyde leads primarily to local genotoxic effects at the site of contact[52].

For cancer effect studies, formaldehyde was long considered as a potential human carcinogen (Group 2A chemical) based on experimental animal studies and limited evidence of human carcinogenicity. However, formaldehyde was reclassified as a human carcinogen (Group 1) by the International Agency for Research on Cancer (IARC) in June 2004 based on "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans"[53,54].

Further more, there are cohort and case-control studies investigating the association between occupational exposure to formaldehyde and Nasopharyngeal Cancer (NPC) and reporting estimates of formaldehyde exposure as well as the most recent meta-analyses[53]. Results of the cohort studies reviewed by Duhayon reported that mortality from NPC was elevated compared with that of the US general population[54]. However, internal comparison analysis using alternative categorization revealed that none of the relative risk for NPC was statistically significantly increased in any category of exposure. Experimental data indicate that in rats, the carcinogenic activity of formaldehyde is associated with cytotoxic/proliferative mechanisms. Therefore protecting from these effects associated with formaldehyde exposure should be sufficient to protect from its potential carcinogenic effects, if any in humans.

Heck and Casanova reviewed the biological evidence that pertains to the issue of leukemia induction by formaldehyde, which includes: (1) The failure of inhaled formaldehyde to increase the formaldehyde concentration in the blood of rats, monkeys, or humans exposed to concentrations of 14.4, 6, or 1.9 ppm, respectively; (2) The lack of detectable protein adducts or DNA-protein cross-links (DPX) in the bone marrow of normal rats exposed to [3H]- and [14C]formaldehyde at concentrations as high as 15 ppm; (3) The lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to [3H]- and [14C] formaldehyde at concentrations as high as 10 ppm; (4) The lack of detectable DPX in the bone marrow of Rhesus monkeys exposed to [14C] formaldehyde at concentrations as high as 6 ppm; (5) The failure of formaldehyde to induce leukemia in any of seven long-term inhalation bioassays in rats, mice, or hamsters; and (6) The failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to airborne concentrations as high as 15 ppm or of mice injected intraperitoneally with formaldehyde at doses as high as 25 mg kg^{-1}[55].

Symptoms of respiratory irritancy and effects on pulmonary function have been examined in studies of populations exposed to formaldehyde (and other compounds) in both the occupational and general environments. In a number of studies of relatively small numbers of workers (38-84) in which exposure was monitored for individuals, there was a higher prevalence of symptoms, primarily of irritation of the eye and respiratory tract, in workers exposed to formaldehyde in the production of resin-embedded fiberglass[56], chemicals and furniture and wood products[57] or through employment in the funeral services industry[58], compared with various unexposed control groups. Due to the small numbers of exposed workers, however, it was not possible to meaningfully examine exposure-response in most of these investigations. In the one survey in which it was considered[59], formaldehyde was a statistically significant predictor of symptoms of eye, nose and throat irritation, phlegm, cough and chest complaints. Workers in these studies were exposed to mean formaldehyde concentrations of 0.17 ppm (0.20 mg m^{-3}) and greater[59,60].

Methods and procedures to control formaldehyde in food and seafood: In order to control or reduces formaldehyde content in food and seafood, several methods and procedures has been taken and proposed. In Hong Kong, food for sale must be fit for consumption as stipulated in the Public Health and Municipal Services Ordinance, Cap. 132. The use of prohibited preservatives such as formaldehyde contravenes the Preservatives in Food Regulations and is liable to a maximum fine of HK$50,000 and imprisonment for 6 months.

Furthermore, great attention to formaldehyde in food and seafood leading to the many research associated formaldehyde determination in order to measure and control formaldehyde amount in food[6,8,18,61]. Wang et al suggested rapid determination of formaldehyde in food products and Chinese herbals based on reaction between formaldehyde and acetyl acetone solution[18]. Many different procedures also has been proposed to determine formaldehyde in seafood such as using High-Performance Liquid Chromatography (HPLC) for formaldehyde determination in squid[7] and solid Phase Microextraction (SPME)-GC-MS for determination in fish[5].

Hong Kong Government also advised to the public to choose only fish that are fresh and avoid those with unusual smell; and avoid buying noodlefish that are stiff (formaldehyde could stiffen flesh of fish). Besides, public also advised to wash and cook food products thoroughly as formaldehyde is water soluble and could dissipate upon heating. The formaldehyde concentration was decreased after roasting and boiling[5]. Boiling also resulted in a large accumulation of DMA and a lesser increase in free FA in squid[36]. The decrease behavior was due to the evaporation of the analyte during cooking process[5].

CONCLUSION

In conclusion, formaldehyde is a chemical hazard that was found in high concentration in seafood and marine fish. This compound was used as food preservatives and additive in seafood product such as caviar and herring. In the others hand, formaldehyde also can produce naturally by the enzymatic activity of trimethylamine oxide aldolase (TMAOase). Many studies showed that formaldehyde exposure can cause dermatitis, eye irritation, respiration irritation, asthma and pulmonary edema. Some studies have found that formaldehyde can cause respiratory cancer and also can increase the rate of leukemia. Furthermore, several methods have been suggested to reduce formaldehyde in food such as cooking and washing. The finding of many health effect of formaldehyde, suggests that the investigation of level of formaldehyde in seafood should be done and also the level of formaldehyde natural production.

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