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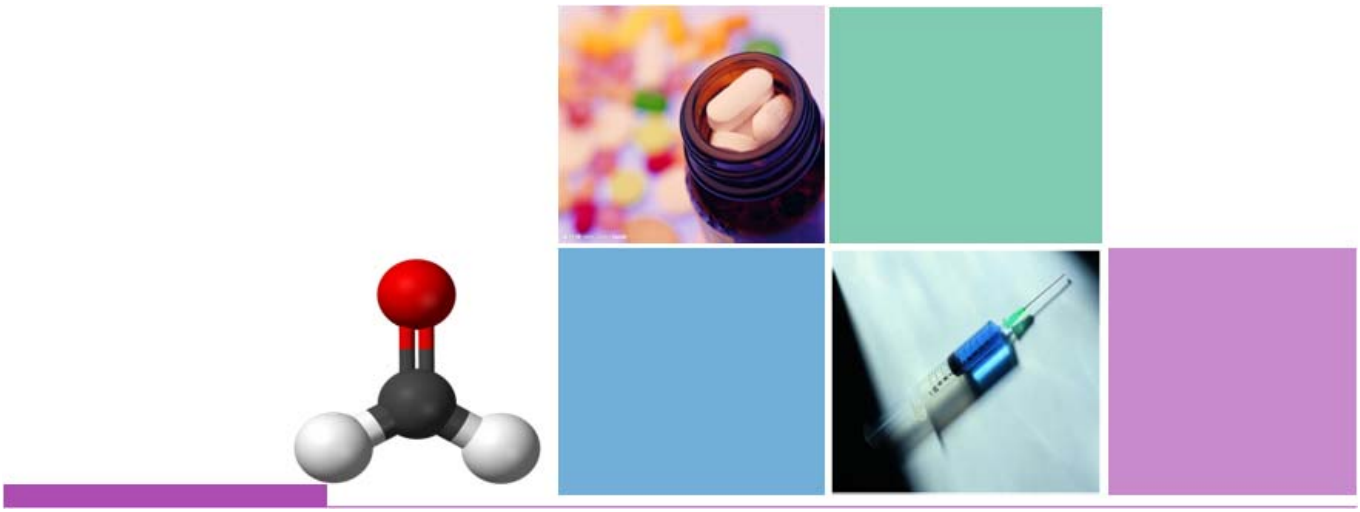

OHSAH

TOXICOLOGY PROFILE

FORMALDEHYDE IN THE HEALTH CARE INDUSTRY

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Summary

This report focuses on formaldehyde in healthcare industry, from chemical and physical properties, use and exposure route in healthcare settings, current monitoring data in healthcare, toxicity and health effects of exposure, current regulations and standards, to control measures that can reduce exposure among workers.

The most important properties of formaldehyde are its biocidal activity, which make it used as sterilant and disinfectant in healthcare; and its volatility, which is why it may be an airborne hazard. Previous monitoring data showed that when certain task is performed, healthcare workers may be over-exposed to formaldehyde.

Formaldehyde is a strong irritant and allergy, which will cause eye and skin irritation, skin sensitization, and occupational asthma. Formaldehyde is one proven carcinogen to animals, and some epidemiological studies revealed elevated cancer rate of respiratory tract among humans. Besides, formaldehyde is known to be a genotoxic substance, which will cause DNA mutation. Its reproductive effects remains controversial, as although some epidemiology studies do showed elevated rate of spontaneous abortion among healthcare workers exposed to formaldehyde, possible chemical and physical confounders make it difficult to get conclusive evaluation.

Due to the health concern, substituting formaldehyde with safer chemicals is necessary whenever applicable. Also, ventilation proves to be capable of reducing exposure level.

Part 1 General Information

Substance name
formaldehyde

CAS number
50-00-0

Synonyms and trade names of formaldehyde products
methaldehyde, methyl aldehydes, methylene glycol, methylene oxide, oxomethane, paraform, paraformaldehyde, methanal, BFV, formol, Fyde, Ivalon, Karsan, Lysoform, Morbicid.

Formula
CH_2O

Some useful chemical and physical properties of formaldehyde are summarized in **Table 1**.

Table 1. Chemical and Physical Property of Formaldehyde [1]

Physical Description	Nearly colorless gas with a pungent, suffocating odor. Often used in aqueous solution.
Molecular Weight	30.0 g/mol
Boiling Point	-21°C
Solubility	Miscible
Flash point[2]	N/A (Gas)
Ionization potential[3]	10.88 eV
RGasD [4]	1.04
Vapor pressure[5]	>1atm
Freezing point	-92.2°C
Upper explosive limit[6]	73%
Lower explosive limit[6]	7%
Conversions	1ppm=1.23mg/m^3

[1]: All data retrieved from NIOSH Pocket Guide to Chemical Hazards (2007).
[2]: Temperature at which liquid phase gives off enough vapor to flash when exposed to and external ignition source. For formaldehyde, since it is gaseous at NTP, so flash point cannot be applied.
[3]: IP is useful for the selection of PID lamps used in some direct reading instruments.
[4]: RGasD: Relative density of gasses referenced to air.
[5]: 20°C
[6]: % by volume

Part 2 Sources of formaldehyde

Natural existence

Formaldehyde exists naturally in the environment, mainly from the combustion of plants and the oxidation of hydrocarbons in the troposphere. It is one of the volatile compounds formed in the early stages of the decomposition of plant residues in the soil (WHO, 1989). Its background concentration level in Canada was measured to be 0.024ppm in the rural environment, and 0.08ppm in urban environment, according to an environmental monitoring study between 1989 and 1998 (Environment Canada, 2001).

Cigarette Smoke

It is estimated that there is 0.38mg of formaldehyde inhaled per pack of cigarettes (Robert S. B., et al, 1984). Sidestream cigarette smoke contains 0.1 to 4.0 ppm formaldehyde (Eatough et al., 1990; Lofrothe et al., 1989).

Production and general use

Formaldehyde is one major product of chemical industry, and is ranked 23rd by volume among commodity chemicals manufactured in U.S (Anon, 1989). It is used mainly in the production of phenolic, urea, melamine and polyacetal resins, plywood, textiles, leather goods, paper and pharmaceuticals.

Use of formaldehyde in healthcare industry

Formaldehyde solutions are used as a fixative in laboratories and morgue (Tweedy J. T., 2005), as well as disinfectant, sterilant and preservative. In Canada, 6% and 2% of formaldehyde consumption are used for fertilizer manufacture and disinfection respectively; by comparison, 92% of the consumption is used for the manufacture of formaldehyde-based glues and the synthesis of other chemicals (Environment Canada, 2001).

U.S. NIOSH received serials of complaints among healthcare workers about irritation and other syndromes. So in response of these complaints, NIOSH conducted monitoring in those healthcare settings. Results were summarized in **table 2** as below. From the table, we can see that among the 15 monitoring cited, only 2 cases were well below any of the exposure limits set up by WorkSafeBC, ACGIH, OSHA and NIOSH, which indicates formaldehyde is one potential occupational hazard in healthcare settings, especially when there are complaints about irritation. From the studies, we can also get: **1)** In two studies, personal breathing area sampling concentration is higher than area sampling, so it is suggested that personal breathing area sampling is a better way of evaluation real exposure situation, **2)** laboratory staff, theatre nurses, employees of dialysis unit and employees of chemical decomposition unit can be exposed to formaldehyde higher than standards, **3)** certain job task may produce peak exposure, so it is possible that 8hrs-TWA is in compliance with the standards, while peak level exceeds ceiling limit.

Table 2. Environmental Monitoring Data of Formaldehyde in Healthcare Settings

Author	Job/task	Exposure level
Binding et al, 1989	Cleaning staff in operating theatres, who used 0.5% formaldehyde as disinfectant.	During short-term of intermediate and final cleaning procedures, peak concentration was measured of up to 0.43ppm. For whole cleaning time, the mean concentration was 0.23ppm.
McGlothlin-J. & Donohue-M, 1979[1]	Employees in Tufts Medical School with angioneurotic edema.	Less than 3ppm (not specified).
Pierre et al, 1983[2]	Histological technicians, including gross dissection, tissue processing, slide preparation and staining.	Forty-four TWA formaldehyde air samples were collected from nine worksites, and the air concentrations ranged from none detected to 0.7ppm, which is below OSHA PEL. However, follow-up questionnaire indicated that formaldehyde was a hazard existed during activities such as tissue disposal, formalin preparation and changing of tissue processor solutions.
Daniel et al, 1992[3]	Employees at nail sculpturing and tanning salon.	Formaldehyde sampling showed a trace concentration (0.014ppm).
Bradley et al, 2006[4]	Surgery department employees, area air-sampling.	Formaldehyde concentration ranges from less than limit of detection (LOD) to 0.017ppm.
Gunter, 1979[5]	Employees of hospital laboratory	All breathing-zone air samples were below LOD.
Chrostek, 1981[6]	Area sampling of McKeesport Hospital, PA (department not specified).	Formaldehyde concentration ranged from 1.9ppm to 2.3ppm, which is well above exposure limits set by WorkSafeBC, ACGIH and NIOSH.
Belanger et al, 1981[7]	Employees of kidney dialysis unit, who frequently reported eye and nose irritation during kidney rinsing.	Formaldehyde concentrations ranged from undetectable to 0.9 part per million, which is above exposure limit by WorkSafeBC, ACGIH and NIOSH.
Chrostek et al, 1981[8]	Workers of plastic decomposition unit.	Formaldehyde concentrations ranged from 0.37ppm to an upper range of 2.93ppm, which is above ceiling limits of WorkSafeBC and STEL of ACGIH, NIOSH and OSHA.
Patnode, 1982[9]	Employees of surgical biopsy hood at the Appalachian Laboratory for Occupational Safety and Health, WV.	Personal breathing zone samples showed average formaldehyde concentrations of 3.6 to 6.7ppm with a peak concentration of 11ppm, well above exposure limits.
Chrostek, 1983[10]	Pathology laboratory where tissue was preserved in a 10% formalin solution, also, organic solvents were used to prepare slides for microscopic evaluation.	After area monitoring, the author concluded that a health hazard did not exist from exposure to organic solvent vapors. But the actual concentration data was not given.
Pryor, 1984[11]	Employees working in dialysis center of the hospital.	Breathing zone samples contained 0.2 to 0.8ppm, area sampling showed concentrations range from less than LOD to 0.61ppm.
Apol, 1985[12]	Pathologists working in histology laboratory, who showed complaining irritation syndrome.	Exposure level of pathologists is 0.50 to 1.23ppm, and general air sample concentration was 0.4ppm. During tissue examination, formaldehyde concentrations ranged up to 0.81ppm for a short term, which is above ACGIH-STEL limit.
Salisbury, 1981[13]	Lab technicians who had complained of headaches,	Lab technicians were exposed to 12.8 ppm of formaldehyde for 30 minutes per week when changing formalin solution in tissue processors,

	inability to concentrate, nausea, and sinus problems.	which is above ceiling limit.
Gunter et al, 1981[14]	Medical and dental students working at a gross anatomy laboratory at the University of Colorado Medical School.	Area air samples showed concentration levels from 0.02 to 2.69ppm, eight samples exceeded the 1ppm WorkSafeBC STEL limit.

[1] NIOSH HHE No. 79-86-675, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=3302&bFlag=3
[2] NIOSH HHE No. 1981-0422-1387, retrieved from http://www.cdc.gov/niosh/hhe/reports/pdfs/1981-422-1387.pdf
[3] NIOSH HHE No. 1990-0048-2253, retrieved from http://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0048-2253.pdf
[4] NIOSH HHE No. 2000-0402-3021, retrieved from http://www.cdc.gov/niosh/hhe/reports/pdfs/2000-0402-3021.pdf
[5] NIOSH HHE No. 79-106-635, retrieved from http://www.cdc.gov/niosh/hhe/reports/pdfs/2001-0066-3019.pdf
[6] NIOSH HHE No. 81-142-892, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=4749&bFlag=0&ID=89
[7] NIOSH HHE No. 81-180-1171, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=4805&bFlag=0&ID=93
[8] NIOSH HHE No. 81-298-944, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=4748&bFlag=0&ID=96
[9] NIOSH HHE No. 82-368-1308, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=6014&bFlag=0&ID=116
[10] NIOSH HHE No. 83-261-1448, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=12296&bFlag=0&ID=129
[11] NIOSH HHE No. 84-427-1613, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=5625&bFlag=0&ID=149
[12] NIOSH HHE No. 85-052-1623, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=6542&bFlag=0&ID=158
[13] NIOSH HHE No. 81-226-1048, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=5494&bFlag=0&ID=268
[14] NIOSH HHE No. 82-045-1108, retrieved from http://www2a.cdc.gov/hhe/select.asp?PjtName=5412&bFlag=0&ID=284

Part 3 Exposure Routes

Inhalation

Formaldehyde is extreme volatile, so inhalation is one major route of exposure. Table 2 above showed occupational monitoring data of airborne formaldehyde in healthcare settings. Exposure to formaldehyde may occur outside work place, such as smoking; emission from fabrics and furnishing; and gas-burning stoves (National Research Council, 1981). Aside from source of its use as disinfectant, the most significant sources of formaldehyde are likely to be pressed wood products made using adhesives that contain urea-formaldehyde (UF) resins (U.S. EPA, 2009). Average concentrations in older homes are generally well below 0.1 (ppm), while in homes with significant amounts of new pressed wood products, levels can be greater than 0.3 ppm (U.S. EPA, 2009).

Dermal

Direct contact of skin and eyes with splashes of formaldehyde liquid. Dermal exposure may be also caused by contact with clothing contaminated with formaldehyde, if the clothing is saturated with formaldehyde. Also, use of formaldehyde/formalin/paraformaldehyde containing cosmetics may cause dermal exposure. However, systematic absorption, including penetration into the circulatory system is estimated to be negligible (WHO, 1989).

Ingestion

Formaldehyde exists naturally in foods, and may occur during food processing, such as fumigation, cooking (as a combustion product), and release from formaldehyde-resin-based tableware (WHO, 1989). Specifically, formaldehyde has been used as a bacteriostatic agent in some foods, such as cheese (Restani, et al, 1992). Formaldehyde level is 3~60 mg/kg in fruit and vegetables, 1mg/kg in milk, and 1~100 mg/kg in shellfish (WHO, 1989). Oral is not one major route of exposure, as the amount of formaldehyde in foods is very small (ATSDR, 1999).

Blood Exchange

This route of exposure is most likely to occur in dialysis or in surgery with assisted circulation, in which the dialysis machine and tubes are disinfected with formaldehyde. In addition, formaldehyde from adsorption or backwashes can enter the patient's bloodstream (WHO, 1989).

Comparison of Relative Significance of Different Routes of Exposure

Based on previous studies, adverse effects of formaldehyde exposure are most likely to be observed primarily following **inhalation**, which is due to the high water solubility of formaldehyde, so it can be absorbed at the upper respiratory tract. **Dermal** route predominately affects the skin itself, and only negligible amount can reach the bloodstream. Exposure to formaldehyde through **ingestion** commonly exists, but most of it is in a bound form. **Blood exchange** is a critical form of exposure if happens, but is very rare.

Part 4 Toxicokinetics

Absorption

Due to its high water solubility, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts. Animal studies showed that 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract of rats (nasal passage) and monkeys (nasopharynx, trachea and proximal regions of the major bronchi) (WHO, 1989).

Generation

In the body, formaldehyde is produced in small quantities as a normal metabolite and also in the oxidative demethylation of xeno-biotics, so it may be found in the liver (IARC, 1995).

Distribution

Because of the rapid metabolizing rate, exposure of human, monkeys or rats to formaldehyde by inhalation does not alter the concentration of endogenous formaldehyde in blood. Intravenous administration of formaldehyde to dogs, cats and monkeys does not result in accumulation of formaldehyde in the blood, because of its rapid conversion to formate ($HCOO^-$). In dogs, orally administered formaldehyde results in a rapid increase in formate levels of the blood. In one isotopic study of rats, 6-hours after inhalation of 14C-formaldehyde, radioactivity was extensively distributed in other issues, with the highest concentration in the oesophagus, followed by the kidneys, liver, intestine and lung, suggesting that absorbed 14C-formaldehyde and its metabolites are rapidly removed by the mucosal blood supply and distributed throughout the body (WHO, 1989).

Metabolism and Bio-transformation

Formaldehyde reacts virtually instantaneously in primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Formaldehyde acts as an electrophile and can react with macromolecules such as DNA, RNA and protein to form adducts or irreversible cross-links (WHO, 1989). Formaldehyde can be oxidized to formate ($HCOO^-$) through three different pathways.

Elimination

Completed oxidized formaldehyde can be exhaled as carbon dioxide. Smaller amounts can be excreted in the urine as formate salts and several other metabolites (WHO Regional Office for Europe, 1987).

Part 5 Health effects

Irritation vs. Allergy

Irritation *results from coming into contact with a substance that irritates the skin, which does not involve excitation of the immune system. Diagnosis of irritation can be achieved by recording exposures and knowledge of possible irritants. Also negative patch test can distinguish irritation from allergic reactions.*

Allergy *is a disorder of the immune system, which is characterized by excessive activation of mast cells and basophils by IgE. One wide used diagnosis method of allergic reaction is "skin testing", also known as "puncture testing" or "patch test", which can determine the kind of substance patient is allergic to.*

a) Irritation

Formaldehyde will cause contact dermatitis and irritation of eyes and upper respiratory tract (Nordmad H., et al, 1984). The threshold for subjective effects varies from 0.1 to 2.5ppm, with most people being affected first in the throat (Cain W. S., et al, 1986). Symptoms in the lower airways, such as cough, chest tightness, and wheeze are observed at concentrations around 5ppm (Weber-Tschopp, A., et al, 1977). If liquid formaldehyde solution is contacted with the eyes, cornea damage and possibly blindness will occur. WHO assessed acute health effects of formaldehyde exposure, most of which are irritation syndromes, and they are summarized in **table 3** as below (WHO, 1989).

Table 3. Effects of formaldehyde in humans after short-term exposure

Concentration (ppm)	Exposure duration	Health effects in general population
0.024	Repeated exposure	Odor detection threshold (10th percentile)
0.15	Repeated exposure	Odor detection threshold (50th percentile)
0.5	Repeated exposure	Odor detection threshold (90th percentile)
0.08~2.5	Single and repeated exposure	Throat and nose irritation threshold
0.5~1	Single and repeated exposure	Eye irritation threshold
0.4~1.6	3~5 hours	Decreased nasal mucus flow rate
2.0	40 minutes on 2 successive days with 10 minutes of moderate exercise on second day	Post-exposure (up to 24 hours) headache
2.0~3.0	Not specified	Biting sensation in eyes and nose
3.0	Single and repeated exposure	Decreased pulmonary function only at heavy exercise
4.1~5.0	30 minutes	Tolerable for 30 minutes with lachrymation
10~20	Not specified	Strong lachrymation, lasting for 1 hour.
30~50	Not specified	Pulmonary oedema, pneumonia, dander to life
50~100	Not specified	Death

b) Sensitization

i) Skin Sensitization

Formaldehyde has been classified as a strong contact allergen on the basis of guinea pig maximization test (Magnusson B., et al, 1970). In most cases, formalin, instead of gaseous formaldehyde, is a potent skin sensitizer (Smith, A. E., 1992). Formalin could trigger type IV, T-cell mediated delayed hypersensitivity, and after sensitization, individuals may react to challenges of as little as 0.01 percent solution (Marzulli F. N., et al, 1973).

ii) Occupational Asthma

Compared with skin and eyes, the sensitization of the respiratory tract is less clear, one possible reason is that the intrathoracic airways appear to be more immune to formaldehyde than skin and eyes (Hendrick, D. J., et al, 1977).

Some studies involving bronchial provocation tests have revealed a handful of cases whose asthma would appear to be related with formaldehyde exposure. One study did bronchial provocation studies on 15 workers occupationally exposed to formaldehyde, and discovered that formaldehyde exposure can cause asthmatic reaction, and the mechanism of inducing asthma could be either hypersensitivity or direct irritant effect, based on reaction time and histamine reactivity tests (Burge, P. S., et al, 1985). Another study of the nursing staff of a haemodialysis unit, who use formalin to sterilize artificial kidney machines, showed that exposure to formalin did not seem to be directly responsible in all cases, however, it might have increased individuals' susceptibility to other provoking agents or induced a hyper-reactive responsiveness of the airways (Hendrick, D. J., 1977). An occupational surveillance among 1,879 healthcare workers in four U.S. states from 1993 to 1997 showed that formaldehyde accounts for 5% of all work-related asthma (WRA), and its substitute, glutaraldehyde, accounts for 9% of all WRAs (Elise P., et al, 2005).

c) Reduced Pulmonary Function

The effects of formaldehyde on pulmonary function have been examined both in rats and in humans. In one study, pulmonary mechanics were investigated in rats immediately after a sub-chronic exposure (8 hrs/day, 5 day/week, 5 weeks in total) to formaldehyde at 5.7 ppm (Saldiva, P. H. N., et al, 1985). It turned out that the sub-chronic exposure had no detectable effect on pulmonary mechanics in the rat. There were several studies concerning pulmonary effects of formaldehyde exposure among humans, and are summarized in **table 4** as below. From these studies, we can see that its pulmonary effects are not as significant at low levels (<2ppm).

Table 4. Summary of studies about pulmonary function effects of formaldehyde

Author	Study population	Results
Schachter, E. N., et al. 1987	15 hospital laboratory workers who were exposed to HCHO with concentration from 0 to 2 ppm.	There were no detectable changes in pulmonary function or in response to methacholine challenge in the workers examined
Witek, T. J., et al. 1987	15 asthmatic volunteers who were exposed for 40min at the concentration of 2.0 ppm.	No significant airway obstruction based on flow-volume and airway resistance measurements. No delayed airway response was discovered. There was a slight and non-significant (p=0.12) decrement of threshold in methacholine inhalation challenge (MIC) test. By contrast, bad odor, sore throat and eye irritation were common during exposure.
Kulle et al., 1987	19 subjects were randomly exposed to 0.0, 1.0, 2.0 and 0.5 or 3.0 ppm at rest, plus 2.0 ppm with exercise for 3 hours each.	No observably significant dose-response relationship between formaldehyde exposure and change in pulmonary function. By comparison, significant dose-response for eye irritation and odor sensation ($p<0.05$) and borderline significance ($p=0.054$) for nose/throat irritation were discovered.
Alexandersson R., et al., 1982	47 subjects exposed to formaldehyde with the mean air concentration of 0.45mg/m^3 (0.37ppm) and 20 unexposed	A reduction in forced expiratory volume ($p=0.04$) and maximum midexpiratory flow ($p=0.04$), as well as an increase in closing volume in percentage of vital capacity ($0=0.002$) were seen after exposure to formaldehyde, suggesting bronchoconstriction. There

	subjects, all of whom were employed at a carpentry shop.	were no significant difference between smokers and non-smokers based on spirometer test and nitrogen wash-out.

However, at higher concentrations (5~30ppm), airborne formaldehyde can severely irritate the lungs, cause chest pain and shortness of breath (CDHS, 2003). Based on this, NIOSH sets IDLH of formaldehyde at 20ppm.

d) Carcinogenicity

There are sufficient animal toxicological data showing that formaldehyde is one animal carcinogen (EPA IRIS, 2009). For example, dose-response relationship for its carcinogenicity illustrated by one of those studies is summarized in **table 5**(Kerns et al. 1983).

Table 5. Dose response data concerning carcinogenicity of formaldehyde

Administered (ppm)	Human equivalent mg/(kg*day)	Tumor incidence
0	0	0/156
2	2	0/159
5.6	5.6	2/153
14.3	14.3	94/140

For evaluating formaldehyde's carcinogenicity to human, although there are a number of epidemiological studies, controversies still exist concerning how valid the results are, because of the weak trend and lack of control. Most of these studies were case-controls and cohorts, but there were a few proportional mortality studies. Those case-control studies focused on tumors of the upper respiratory tract or nasopharynx, lung cancer, or bladder cancer, from either occupational or residential exposure to formaldehyde. However, they were confounded with concomitant exposure to other pollutants, such as wood dust and other organic solvents. In addition, although an excess of nasal or nasopharyngeal cancers were reported, it is still lack of statistical significance to draw clear conclusion (Smith, A. E., 1992). For the cohort studies, they focus on relating occupations, such as chemical workers, embalmers, male pathologists, anatomists, textile workers, resin works, abrasive manufactures and groups of industrial works to cancers, such as Hodgkins disease, leukemia, lung, nose, prostate, bladder, brain, colon, skin and kidney cancer. However, for some of them, there was no statistically significance or biological plausibility of formaldehyde, which make it possible that the results were due to random variation or factors other than formaldehyde (Smith, A. E., 1992). One most recent study in 2002 by Marsh G. M., et al revealed certain relationship between pharyngeal cancer, nasopharynx cancer and formaldehyde exposure, but still, no dose-response relationship was found, thus making the evaluation of formaldehyde's human carcinogenicity uncertain. I selected most recent studies with largest study population, and summarized them in **Table 6** as below.

Table 6. Summary of epidemiology studies concerning carcinogenicity effects of formaldehyde

Author	Study type	Study population	Results	Comments
Marsh G. M., et al, 2002	cohort and case-control	7328 workers employed at a plastic-producing plant from 1941~1984.	Statistically significant 2.23-fold and 5-fold excesses for pharyngeal cancer (PC) and Nasopharynx Cancer (NPC), respectively. However, no dose-response relationship was revealed, as standardized mortality ratio for all PC and NPC were greater among short-term than long-term workers.	One limitation was that more than 50% of the cohort workers worked at the plant for less than 1 year, which increased the likelihood that pre-occupational exposure might exist.
Hansen J., et al, 1995	cohort	Men with cancer, whose longest work experience had been in companies where there was exposure to formaldehyde at least 10 years before diagnosis in Denmark.	There are no elevated standardized proportionate incidence ratios (SPIR) of lung cancer among formaldehyde exposed group. Significantly elevated risks were found for cancers of colon, kidney and sino-nasal cavities. Also, among workers with no probable exposure to wood dust, relative risk (RR) of sino-nasal cavities was 3.0.	The study unraveled one major confounder of wood dust.
Stayner L. T., et al, 1988	cohort mortality study	11,030 workers exposed for at least three months to formaldehyde in three garment facilities.	Statistically significant excess of mortality from cancer of buccal cavity and connective, and statistically non-significant excess in mortality for cancers of trachea, bronchus and lung, pharynx, bladder, leukemia and aleukemia.	Relatively small numbers, and there are possible confounding factors.
Roush et al., 1987	case control study	198 persons with sino-nasal cancer (SNC) and 173 persons with NPC. 605 controls.	Odds ratio for those with probable exposure to the high levels of 20+ years was 2.3 for NPC.	No adjustment for confounders.
Blair A., et al, 1986	cohort	26,561 workers of 10 formaldehyde-producing or using facilities.	No significant and dose-consistent risk of elevated cancer rate was found. There is a slight excess of Hodgkin's disease, lung, prostate gland, NPC, oropharynx. The overall data provided little evidence that mortality from cancer is associated with formaldehyde exposure at levels experienced by workers in the study.	Adjusted for age, but not other confounders.
Hayes et al, 1985	case-control	The case group was 116 males with nasal and paranasal sinus tumors, control group was 259 males.	Mean RR for between formaldehyde exposure and the risk of nasal cancer was 2.2.	Taken histologic type of tumor, history of tobacco use, and occupational exposure to wood dust.

Consequently, based on the valid animal studies and ambiguous result of human studies, EPA IRIS classified formaldehyde as "B1, probable human carcinogen"; IARC classified it as "1, carcinogen to humans"; and ACGIH classified it as "A2, suspected human carcinogen".

e) Mutagenicity and Genotoxicity

Formaldehyde is known to be a genotoxic substance, as it will induce DNA-protein cross-links as the primary DNA lesion. In addition, there are studies showing mutagenic effects of formaldehyde on microorganisms and mammalian cells, which suggests formaldehyde is one mutagen (EPA IRIS, 2009). Treatment of L5178Y cells with formaldehyde for 2 hours caused a clear and concentration-related mutagenic effect in the mouse lymphoma assay, its mutagenicity can trigger small-scale chromosome rearrangements, such as deletions or re-combinations (Speit and Merk, 2002).

f) Reproductive effects

There are controversies around the issue whether formaldehyde has potential reproductive effects. One animal study found that formaldehyde will cross the placental barrier in mice (Katakura et al., 1993). However, some scholars think that because of the rapid metabolizing and detoxifying rate of formaldehyde, it is unlikely to reach the reproductive system in humans in concentrations sufficient to cause damage (James J. Collins, et al., 2001).

There are studies concerning whether formaldehyde might harm pregnancy or the reproductive system, however the results are mixed and complicated, because of the possible confounders, such as exposure to other chemicals not measured, bias in exposure assessment, small sample size, lack of dose-response relationship and so on. Results as well as limits of these studies were summarized in **Table 7**

Table 7. Summary of studies about reproductive effects of formaldehyde

Researcher	Study population	Results	Comments
Taskinen H. K., et al., 1999	Cohort study of 699 female wood workers who gave birth during 1985 to 1995	Exposure to formaldehyde was associated with delayed conception and increased risk of SAB[1]. No significant development effect of solvent vapor, dust and wood dust was found.	Adjusted for confounders, such as employment status, smoking, drinking, previous children etc. Unraveled the interference of solvent vapor, dust and wood dust.
Taskinen H. K., et al., 1994	Case-control study of women working in laboratories in Finland: 206 SAB cases, 329 controls; 36 malformations cases, 105 controls.	Increased rates of SAB among women reporting exposure to formalin 3~5days/week. But no association with malformations.	No adjustment for other possible lab toxicants, such as toluene, xylene, etc.
Axelsson et al., 1984.	Cross-sectional study of 745 female workers at university labs between 1968 and 1979.	SAB rate in women exposed to formaldehyde was higher than controls (RR=3.3).	No adjustment for confounders.
Hemminki et al., 1982	Cohort study of 1143 pregnancies in Finnish hospital sterilizing staffs and 1179 controls of pregnancies in nursing auxiliary.	No association between formaldehyde exposure and increased rate of SAB was found (RR=1.0).	Adjusted for age, decade of pregnancy, smoking, alcohol, coffee and ethylene oxide exposure.

[1]: Spontaneous abortion

Formaldehyde is not included in Reproductive and Development Toxicant, a report published by the U.S. General Accounting Office (GAO) in 1991, which listed 20 chemicals which were widely acknowledged to have reproductive and developmental consequences.

Part 6 Analysis of Formaldehyde in Air

The most widely used analysis methods for determining formaldehyde concentration in air are based on spectrophotometry, with an accuracy of 10~30μg/m^3 (8~24ppb), gas chromatography, or high performance liquid chromatography (HPLC), with an accuracy of 2μg/m^3 (1.6ppb). Both active and passive sampler can be used to collect airborne samples.

Commonly used sampling and analyzing methods are summarized in **table 8** as below.

Table 8. Sampling and analytic methods for airborne formaldehyde

Sample Preparation	Analysis method	Detection Limit (ppm)	Notes
Draw air through polytetrafluorethylene filter and impingers, each treated with sodium bisulfate solution; develop color with chromotropic acid and sulfuric acid; read absorbance at 580 nm.	Visible absorption spectrometry	0.02	NIOSH standard method
Draw air through solid sorbent tube treated with 10% 2-(hydroxymethyl) piperidine on XAD-2; desorb with toluene	Gas-chromatography with flame ionization detection	0.2	NIOSH standard method
	Gas-chromatography with nitrogen selective detection	0.016	OSHA standard method
Draw air through silica gel coated with acidified 2,4-dinitrophenylhydrazine reagent	High-performance liquid chromatography/UV detection	0.0016	OSHA/NIOSH standard method
Passive monitor (Du Pont Pro-Teck® Formaldehyde Badge or 3M model 3721 monitor) for at least 2 ppm*h, analyze according to manufacture's specifications	Chromotropic acid test	0.08	OSHA standard method

By comparing the limit of detection with exposure limit, we can see that the analytic method is sufficient for compliance purpose.

Part 7 Regulations

Hazard Classifications for Formaldehyde

Table 9 summarized hazard classification of formaldehyde by different regulatory agencies.

Table 9. Summary of hazard classification of formaldehyde

System	Substance	Classification or Note
Canadian WHMIS classification criteria	Formaldehyde in its solution	B3 "Flammable and combustible material – Combustible liquid" D1A "Poisonous and infectious material – Immediate and serious effects – Very toxic" D2A "Poisonous and infectious material – Other effects – Very toxic" D2B "Poisonous and infectious material – Other effects – Toxic" E "Corrosive material".
CSST	Formaldehyde	A "compressed gas" B1 "flammable gas" D1A "very toxic substance causing immediate serious effects for its acute toxic effects" D2A "toxic material causing other toxic effects for its carcinogenicity" D2B "toxic material causing other toxic effects for eye irritation in humans and mutagenicity in animals"
OSHA	Formaldehyde	Formaldehyde meets the criteria for hazardous material, as defined by 29 CFR 1910. 1200
European Commission Joint Research Centre, Institute for Health and Consumer Protection (EC-JRC-IHCP)	Formaldehyde solution	***EU Risk Phrases***: 23/24/25-Toxic by inhalation, in contact with skin and if swallowed. 34-Cause burns. 40-Limited evidence of a carcinogenic effects. 43-May cause sensitization by skin contact. ***EU Safety Phrases***: 1/2-Keep locked up and out of the reach of children. 26-In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. 36/37/39-Wear suitable protective clothing, gloves and eye/face protection. 45-Incase of accident or if you feel unwell, seek medical advice immediately (show the label where possible). 51-Use only in well-ventilated areas. ***EU Comments***: *Concentration≥25%*: Toxic; Toxic by inhalation, in contact with skin, and if swallowed. Causes burns. Limited evidence of a carcinogenic effect. May cause sensitization by skin contact. *Concentration≥5% but <25%*: Harmful; Harmful by inhalation, in contact with skin and if swallowed. Irritating to eyes, respiratory system and skin. Limited evidence of carcinogenic effect. May cause sensitization by skin contact. *Concentration≥1% but <5%*: Harmful; Limited evidence of a carcinogenic effect. May cause sensitization by skin contact. *Concentration≥0.2% but <1%*: Irritant; May cause sensitization by skin contact.

Exposure limits

Table 10 summarized exposure limits of formaldehyde set up by four jurisdictions and agencies within or outside of Canada.

Table 10. Exposure limits of formaldehyde

Jurisdiction	WorkSafeBC	ACGIH	OSHA PEL	NIOSH
TWA[1]	0.3ppm	N/A	0.75ppm	0.016ppm
STEL [2]	1ppm	0.3ppm	2ppm	0.1ppm
Ceiling [3]	1ppm	N/A	N/A	N/A
Notations	A2[4];1[5];S[6]	SEN [7]; A2 [8]	N/A	N/A

[1]: 8-hrs time weighted average airborne concentration.
[2]: 15 min short time exposure limit.
[3]: maximum allowable concentration, which may not be exceeded even momentarily.
[4]: same as class A2 in ACGIH notation for carcinogenicity, suspected human carcinogens.
[5]: same as class 1 in IARC carcinogen classification, carcinogenic to humans.
[6]: the substance is a sensitizer under OHS regulation section 5.57(1)
[7]: It is potential that the agent will produce sensitization, as confirmed by animal or human data.
[8]: suspended human carcinogen.

EPA IRIS intake guidelines (RfD & RfC)

RfD: 0.2 mg/(kg*day)
RfC: N/A
Dose-response relationship: $NOAEL_{rats, oral}$ is 15 mg/(kg*day), Health effects observed among high-dose groups include: decrease in drinking food and water intake, decrease of body weight, increase in kidney weight among female rats and brain weight among male rats. There are formaldehyde toxicity studies among rats, mice and dogs, but higher NOAELs were obtained. So the NOAEL of 15 mg/(kg*day) is applied combined with an UF of 100 (inter- and intra- species) and an MF of 1, which make RfD 0.2 mg/(kg*day).

NFPA 704

Health 3 (short exposure could cause serious temporary or residual injury); flammability 2 (must be moderately heated or exposed to relative high ambient temperature before ignition can occur); reactivity 2 (undergoes violent chemical change at elevated temperatures and pressures, reacts violently with water, or may form explosive mixtures with water).

Immediately Dangerous to Life or Health concentration (IDLH)

NIOSH sets up IDLHs for formaldehyde as 20ppm, based on the assumption that it is the maximum airborne concentration from which a worker could escape without injury or irreversible health effects, in the event of failure of respiratory protection equipment.

Part 8 Control Measure

NIOSH's prioritizing of control measures:

".....Controlling exposures to occupational hazards is the fundamental method of protecting workers. Traditionally, a hierarchy of controls has been used as a means of determining how to implement feasible and effective controls. One representation of this hierarchy can be summarized as follows:

- ***Elimination***
- ***Substitution***
- ***Engineering controls***
- ***Administrative controls***
- ***Personal protective equipment***

The idea behind this hierarchy is that the control methods at the top of the list are potentially more effective and protective than those at the bottom. Following the hierarchy normally leads to the implementation of inherently safer systems, ones where the risk of illness or injury has been substantially reduced.

Requriement of Formaldehyde Control

According to WorkSafeBC OHS Regulation Section 5.57:

Since formaldehyde is identified as A2, suspected human carcinogen and skin sensitizer, the employer must "replace it, if practicable, with a material which reduces the risk to workers". If it is not practicable to substitute a material which reduces the risk to workers, the employer must "implement an exposure control plan to maintain workers' exposure as low as reasonably achievable below the exposure limit established under section 5.48". And the exposure control plan must meet the requirements of section 5.54.

Substitution

Possible substitution methods include:

- Use safer substitutes whenever possible, e. g., diluted bleach solutions can be used as disinfectants to substitute formaldehyde, and ethyl alcohol, polyethylene glycol, or phenoxyethanol can be used as fixatives or preservatives (CDPH, 2003).

- WorkSafeBC recommends that an exposure control plan as per OHS Reg 5.57 (2) should be implemented, so based on the regulation, formaldehyde has to be substituted. If it is not practicable, then the employer must implement an exposure control plan to maintain worker's exposure as low as reasonably achievable below the applicable exposure limit (WorkSafeBC, 2001).

- It should be noticed that many of the substances used as a substitute have turned out to be more potent skin sensitizers (Smith, A. E., 1992).

Ventilation

- Operations which involved the use of formaldehyde should be performed where there is sufficient air exchange with fresh air (mechanical and externally vented ventilation system, and appropriate air-cleaning devices). Also, make sure that ventilation system does not re-circulate formaldehyde vapors.

- Conduct regular maintenance on ventilation systems and ensure that they are functioning properly.

Administrative measures

- Identify regulated areas where formaldehyde concentrations exceed the TLV-TWA or -STEL, then post warning signs, and limit the access to the area. Also, according to NIOSH guideline, eye wash fountains and facilities should be set up in areas where splashing may occur with solutions that contain 0.1% formaldehyde. If solutions of higher concentration are used, then emergency showers located within 10 seconds of the splash area should be set up (Title 8, Section 5162, CCR, 2009).

- Educate employees about formaldehyde heath hazards and symptoms of overexposure. Emphasize the importance of reporting symptoms early.

- Instruct employees on the use of safe work procedures. e.g., use of laboratory fume hoods when working with open containers of formaldehyde or specimens preserved in formaldehyde, cap storage containers immediately when formaldehyde is not in use, etc.

- Demonstrate the proper use and maintenance of fume hoods and other local exhaust ventilation systems.

- Explain the functions and limitations of PPE, as well as demonstrating how to use them properly.

- Instruct employees on how to respond to spills and emergencies, and on safe clean-up procedures.

- Ensure that the workers will wash their hands thoroughly after using formaldehyde, even if gloves are worn.

Minimize exposure from spills and contaminated material

- Set up preventive maintenance program to perform frequent inspect to detect leaks and spills.

- Repair all leaks and clean up spills promptly, as evaporation rate of formaldehyde is great.

- Place formaldehyde contaminated waste and debris, or formaldehyde treated specimen for disposal in sealed, labeled container.

- Use formaldehyde neutralization pads or sheets where small spills or drips may occur on work surfaces.

Personal Protection Equipment

- NIOSH recommended PPE and selection of respirator is presented in **table 11** as below.

Table 11. NOISH recommended personal protective equipment

Skin protection	Wear appropriate personal protective clothing to prevent skin contact.
Skin wash	The worker should immediately wash the skin when it becomes contaminated.
Eyes protection	Wear appropriate eye protection to prevent eye contact.
Remove of clothing	Work clothing that becomes wet or significantly contaminated should be removed and replaced
Routinely change of clothing	No recommendation is made specifying the need for the worker to change clothing after the workshift
Need of facilities	Eyewash fountains should be provided in areas where there is any possibility that worker could be exposed to the substances; this is irrespective of the recommendation involving the wearing of eye protection. And facilities for quickly drenching the body should be provided within the immediate work area for emergency use where there is a possibility of exposure.
Selection of respirator	***At concentrations above the NIOSH REL***: Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode; or any supplied-air respirator that has a full-facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode. An assigned protective factor (APF) of 10,000 is required. ***For escape purposes***: Any air-purifying, full-facepiece respirator (gas mask) with a chin-style, front- or back-mounted canister providing protection against the compound of concern; or any appropriate escape-type, self-contained breathing apparatus. An APF of 50 is required.

- California Department of Health Services recommended that gloves made of nitrile, neoprene, butyl rubber or polyethylene laminate should be used to protect hands against incidental contact with formaldehyde, and gloves made of latex may not provide adequate protection and may cause allergic reactions (CDHS, 2003). According to

California Code of Regulation, for employees who are required to change form work clothes to protective clothing, changing room with storage facilities for street clothes and separate storages facilities for the protective clothing should be provided (Title 8, Section 3367, CCR, 2009).

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