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Review

Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms

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ABSTRACT

Formaldehyde is an economically important chemical, to which more than 2 million U.S. workers are occupationally exposed. Substantially more people are exposed to formaldehyde environmentally, as it is generated by automobile engines, is a component of tobacco smoke and is released from household products, including furniture, particleboard, plywood, and carpeting. The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen that causes nasopharyngeal cancer and also concluded that there is "*strong but not sufficient evidence* for a causal association between leukemia and occupational exposure to formaldehyde". Here, we review the epidemiological studies published to date on formaldehyde-exposed workers and professionals in relation to lymphohematopoietic malignances. In a new meta-analysis of these studies, focusing on occupations known to have high formaldehyde exposure, we show that summary relative risks (RRs) were elevated in 15 studies of leukemia (RR = 1.54; confidence interval (CI), 1.18–2.00) with the highest relative risks seen in the six studies of myeloid leukemia (RR = 1.90; 95% CI, 1.31–2.76). The biological plausibility of this observed association is discussed and potential mechanisms proposed. We hypothesize that formaldehyde may act on bone marrow directly or, alternatively, may cause leukemia by damaging the hematopoietic stem or early progenitor cells that are located in the circulating blood or nasal passages, which then travel to the bone marrow and become leukemic stem cells. To test these hypotheses, we recommend that future studies apply biomarkers validated for other chemical leukemogens to the study of formaldehyde.

Contents

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Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATSDR, Agency for Toxic Substances and Disease Registry; BFU-E, burst-forming unit-erythroid; CA, chromosomal aberrations; CDC, Centers for Disease Control and Prevention; CFU-GEMM, colony-forming-unit–granulocyte, erythroid, monocyte, macrophage, megakaryocyte; CFU-GM, colony-forming-unit–granulocyte-macrophage; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DPCs, DNA–protein crosslinks; EPA, Environmental Protection Agency; FEMA, Federal Emergency Management Agency; FISH, fluorescence *in situ* hybridization; GNP, Gross National Product; HL, Hodgkin lymphoma; HSE, Health and Safety Executive, Great Britain; IARC, International Agency for Research on Cancer; ILO, International Labour Organization; IPCS, International Programme on Chemical Safety; IRIS, Integrated Risk Information System; JSOH, Japan Society for Occupational Health; LL, lymphocytic leukemia; MAC, maximum allowable concentration; MDS, myelodysplastic syndromes; ML, myeloid leukemia; MM, multiple myeloma; MN, micronuclei; MHPRC, Ministry of Health, People's Republic of China; MRL, minimal risk level; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; NTP, National Toxicology Program; OEHHA, Office of Environmental Health Hazard Assessment California EPA; OELs, occupational exposure limits; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; ppb, parts per billion; ppm, parts per million; REL, recommended exposure limits; RR, relative risk; RTECS, Registry of Toxic Effects of Chemical Substances; SCEs, sister chromatid exchanges; S.D., standard deviation; S.E., standard error; SPIR, standardized proportionate incidence ratios; STEL, short-term exposure limit; TLV, threshold limit value; TWA, time-weighted average; UFFI, urea-formaldehyde foam insulation; WHO, World Health Organization.

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1. Background on formaldehyde and human exposure levels

1.1. History and chemistry of formaldehyde

Formaldehyde is the most simple yet most reactive of all aldehydes, with the chemical formula CH_2O [1,2]. It exists as a colorless gas at room temperature and has a strong pungent smell. Aleksandr Butlerov synthesized the chemical in 1859, but it was August Wilhelm von Hofmann who identified it as the product formed from passing methanol and air over a heated platinum spiral in 1867. This method is still the basis for the industrial production of formaldehyde today, in which methanol is oxidized using a metal catalyst. By the early 20th century, with the explosion of knowledge in chemistry and physics, coupled with demands for more innovative synthetic products, the scene was set for the birth of a new material–plastics.

Casein formaldehyde became popular in the manufacturing of buttons, buckles, and knitting needles, and was fundamental for the production of the first completely synthetic plastics—*phenolic resins*, which were made by condensing phenol and formaldehyde in the presence of a catalyst. Initially used to make electrical and automobile insulators and other heavy industrial products, phenolic resins were widely used during the 1920–1940s to produce consumer appliances like toasters and radios. In the 1920s, *urea formaldehyde*, a colorless resin similar to phenolic resin, was developed and used to make picnic-ware, lampshades, varnishes, laminates and adhesives. In the 1970–1980s, urea-formaldehyde foam insulation (UFFI) was applied to thousands of North American homes. Subsequently, *melamine formaldehyde* resins, which closely resembled urea-formaldehyde plastics, except are more resistant to heat, water and detergents, were developed in the mid-1930s. With their porcelain-like appearance, they became the raw materials for cups, saucers and other domestic items. Casein formaldehyde, phenolic resins, urea formaldehyde and melamine formaldehyde have played important roles in the production of domestic and industrial goods that have become vital to everyday life.

1.2. Economic importance of formaldehyde

Formaldehyde is an economically important chemical with an annual production of approximately 46 billion pounds worldwide. According to the Report on Carcinogens (11th Edition, National Toxicology Program, NTP) [1], formaldehyde ranks 25th in overall U.S. chemical production with more than 11 billion pounds produced each year. Formaldehyde and goods containing the chemical reportedly account for more than 5% of the annual U.S. Gross National Product (GNP), which is about $500 billion out of a GNP exceeding $10 trillion [2]. Formaldehyde production has increased steadily in China in recent years, with 7.5 million tons (16.5 billion pounds) of formaldehyde produced in 2007 [3]. In Japan, approximately 100,000 to 1 million tons of formaldehyde were produced or imported in 2001 [4,5].

Commercially, formaldehyde is manufactured as an aqueous solution called *formalin*, usually containing 37% by weight of dissolved formaldehyde. It is commonly used as a tissue preservative or as a bactericide in embalming fluid and medical laboratories. Formaldehyde is primarily used in the production of phenol- or urea-formaldehyde resins, plastics and chemical intermediates. Such resins are commonly used in everyday products as previously stated above. Formaldehyde is also widely used in molding compounds, glass wool and rock wool insulation, decorative laminates and textile treatments. Formaldehyde is now extensively used by industries across the globe. Regulatory decisions regarding formaldehyde, such as occupational exposure limits (OELs) and drinking water standards, have an economic impact that runs into the millions, if not billions, of dollars.

1.3. Human exposure to formaldehyde

Given its economic importance and widespread use, many people are exposed to formaldehyde environmentally and/or occupationally. Occupational exposure involves not only individuals employed in the direct manufacture of formaldehyde and products containing it, but also those in industries utilizing these products, such as construction.

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1.3.1. Occupational exposure and safety standards

The Occupational Safety and Health Administration (OSHA) has estimated that approximately 2.1 million workers in the U.S. [6] and many more in developing countries are occupationally exposed to formaldehyde. The exposed workers, commonly found in resin production, textiles or other industrial settings, inhale formaldehyde as a gas or absorb the liquid through their skin. Other exposed workers include health-care professionals, medical-lab specialists, morticians and embalmers, all of whom routinely handle bodies or biological specimens preserved with formaldehyde.

The formaldehyde occupational exposure limits of many countries are available on the International Labour Organization (ILO) [7] website and through the Registry of Toxic Effects of Chemical Substances database (RTECS #: LP8925000) maintained by National Institute for Occupational Safety and Health (NIOSH) [8]. Updated limits as well as the limits for several countries not included in the NIOSH document, were compiled using data from the most recently available government publications [8–18], and are described in Table 1. The U.S. OSHA has established the following standards that have remained the same since 1992: the permissible exposure limit (PEL) is 0.75 ppm (parts per million) in air as an 8-h time-weighted average (8 h TWA) and the short-term (15 min) exposure limit (STEL) is 2 ppm [14]. The American Conference of Governmental Industrial Hygienists (ACGIH) recommended threshold limit value (TLV) is 0.3 ppm as an 8 h TWA [17]. The U.S. NIOSH recommends much lower exposure limits of 0.016 ppm (8 h TWA) and 0.1 ppm (STEL) [18], above which individuals are advised to use respirators if working under such conditions. The Agency for Toxic Substances and Disease Registry (ATSDR) has established a chronic inhalation minimal risk level (MRL) of 0.04 ppm based on respiratory effects in humans [19]. The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. Repeated contact with liquid solutions of formaldehyde has also resulted in skin irritation and allergic contact dermatitis in humans [20].

Among the countries listed in Table 1 there is a general trend of decreasing OELs over time. Australia, though its current OEL is 1 ppm TWA and 2 ppm STEL [13], is now in the process of adopting new standards, with proposed OEL TWA and STEL values of 0.3 and 0.6 ppm, respectively [21]. Both Germany and Japan recently approved their current TWA limits, having reduced their original limits from 0.5 ppm [21] to 0.3 and 0.1 ppm, respectively [8,11]. Canada's OEL is regulated by individual provinces, with a national TLV of 0.3 ppm [9]. For example, the TWA value for British Columbia was standardized at 0.3 ppm and for Ontario at 1 ppm [22]. Among all of the countries listed in Table 1, the United Kingdom maintains the highest OEL TWA and STEL at 2 ppm [10]. The United States also continues to retain relatively high OELs, established more than 15 years ago. In many countries actual occupational exposures to formaldehyde may be higher than the OEL values, if such limits are not enforced.

1.3.2. Environmental exposure and ambient levels

Although environmental exposure to formaldehyde typically occurs at much lower levels than occupational exposure, a greater number of people are exposed to these lower levels in their daily lives. Environmental sources of formaldehyde include: (1) off-gassing from new mobile homes (such as the trailers provided to victims of Hurricane Katrina); (2) automobile engines [23], especially those burning biofuels [24]; (3) smoke from cigarettes and the burning of forests and manufactured wood products [25,26]; and (4) various consumer products such as furniture, carpeting [2], fiberglass, permanent press fabrics, paper products and some household cleaners [26]. Of these, the most significant source of global formaldehyde exposure is indoor air pollution from modern home furnishings [27] and incomplete fuel combustion in older homes, where air concentrations could exceed occupational levels [28–30]. Formaldehyde is also formed in the early stages of residual plant decomposition in the soil and in the troposphere during oxidation of hydrocarbons that react with hydroxyl radicals and ozone. It ultimately becomes part of smog pollution [31].

1.3.2.1. Indoor air concentration. Homes containing large amounts of pressed wood products such as hard plywood wall paneling, particleboard, fiberboard, and UFFI often have elevated levels of formaldehyde emissions exceeding 0.3 ppm [32]. Since 1985, the Department of Housing and Urban Development has only allowed

Table 1
Current formaldehyde occupational exposure limits (OEL) of several countries

Country	OEL (ppm)			Reference
	TWA	STEL[e]	TLV	
Australia	1	2		NPI, 2007 [13]
Canada[a]			0.3	CCOHS, 2006 [9]
China[b]			0.4	MHPRC, 2007 [12]
Germany	0.3			NIOSH, 2006 [8]
Japan	0.1			JSOH, 2007 [11]
Sweden	0.5		1	SWEA, 2005 [16]
South Africa	1	2		SAIOH, 2006 [15]
United Kingdom	2	2		HSE, 2007 [10]
United States				
PEL[c]	0.75	2		OSHA, 1992 [14]
REL[d]	0.016	0.1	0.3	NIOSH, 2005 [18]; ACGIH, 2002 [17]

[a]Canadian OEL are similar to the TLV by ACGIH in many provinces but regulated differently within each province.
[b]China only has the maximum allowable concentration (MAC), which is equivalent to TLV. As of 2007, MAC = 0.5 mg/m^3 (~0.4 ppm).
[c]The federal standard is called "permissible exposure limit" (PEL) instead of "OEL".
[d]Recommended exposure limits (RELs as TWA and STEL) were recommended by NIOSH, and TLV by ACGIH.
[e]The procedure for obtaining STEL measurements for each country varies by jurisdiction, with most countries defining "short-term exposure limits" at 30-min periods, with the exception of the U.S., which has adopted 15-min periods.

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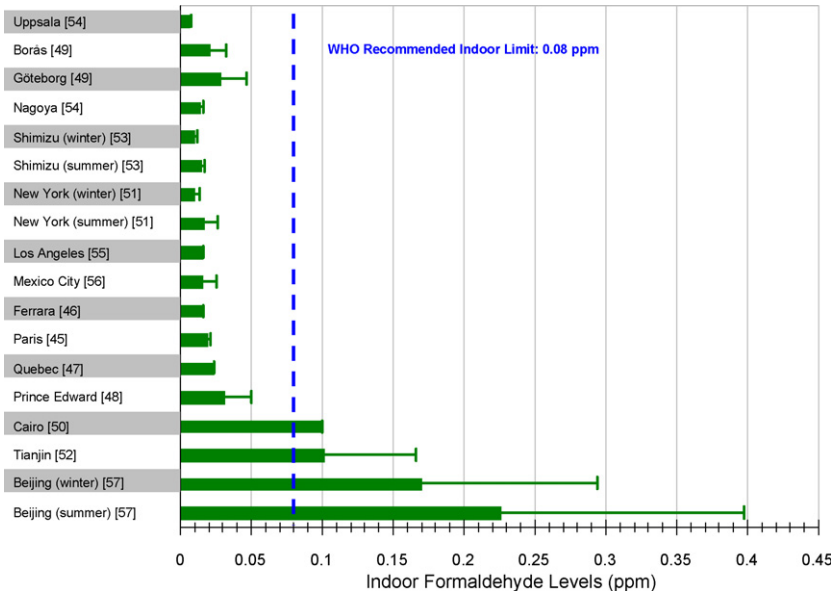

Fig. 1. Indoor air formaldehyde concentrations of households in various cities. The mean levels are represented by bars with standard deviation lines, if available, as reported by the original studies. All values are compared to the WHO recommended limit of 0.08 ppm, represented by the vertical dashed line.

the use of plywood particleboard that conforms to the 0.4 ppm formaldehyde emission limit in the construction of prefabricated and mobile homes [33]. Formaldehyde levels generally decrease as products age. In older homes without UFFI, concentrations of formaldehyde emissions are generally well below 0.1 ppm [32]. This value is close to the indoor limit, 0.1 mg/m^3 (0.08 ppm), recommended by the World Health Organization (WHO) [34], the limit followed by many other countries including the UK [35], Japan [36], and China [37]. Other countries, such as Australia [38], Germany [39], Canada [40], and Singapore [41], have an indoor limit of 0.1 ppm similar to the WHO recommended value. Unfortunately, the U.S. still lacks a national indoor standard and government guidelines regarding indoor ambient formaldehyde exposure [42]. However, the California EPA's Office of Environmental Health Hazard Assessment (OEHHA) has an indoor limit recommendation of 27 ppb (parts per billion) as reported in two documents published by California Air Resources Board [43,44].

Worldwide indoor air concentrations of formaldehyde for several countries [45–57] are shown in Fig. 1. The indoor mean levels of most cities were below or close to 0.08 ppm, the WHO recommended limit, with an exception of Beijing [57], which had reported levels (mean ± S.D., 0.17 ± 0.12 ppm winter, 0.23 ± 0.17 ppm summer) more than twice that value. Three studies observed that seasonal variations have resulted in higher indoor formaldehyde concentrations during the summer due to increased off gassing promoted by the warmer temperatures [51,53,57]. A Quebec study [58] from occupational settings (not shown in Fig. 1), however, reported that higher exposures actually occurred during the winter season and the geometric mean level (0.28 ppm) of the wood panel industry was much higher than all non-occupational indoor levels shown in Fig. 1. It should be noted that these indoor levels were reported directly from the original studies and might have been measured by different methods or from different sampling sources, etc., which could contribute to the possible discrepancies seen here (Fig. 1) and in the following outdoor concentrations (Table 2).

1.3.2.2. Outdoor air concentration. The ambient formaldehyde levels of various cities and countries across the globe are detailed in Table 2. Exposure levels greater than 20 ppb occur in large cities such as Houston, U.S. [59]; Mexico City, Mexico [60,61]; and Cairo, Egypt [50]; and actually exceed the NIOSH recommended exposure level for the workplace of 0.016 ppm (=16 ppb) [18]. Some of the lowest formaldehyde exposure levels can be found in the remote regions of Nunavut, Canada [62] and Lille Valby, Denmark [63], a probable reflection of natural formaldehyde background levels of around 0.4–1.2 ppb. The California OEHHA has set a chronic reference formaldehyde exposure level of 2 ppb [64]. The reference concentration of atmospheric formaldehyde for Japan [5] is recommended to be 10 ppb, and outdoor city levels ranged from 1.1 to 4.7 ppb [53,65], compared with 2.5–3.2 ppb in rural, suburban and urban areas in Japan [5].

Small amounts of formaldehyde are naturally produced in most organisms, including humans, as a metabolic byproduct [1], and are physiologically present in all bodily fluids, cells and tissues. The endogenous concentration in the blood of humans, monkeys and rats is approximately 2–3 mg/L (0.1 mM) [66,67]. Formaldehyde is also found in foods, either naturally or as a result of contamination [68]. Therefore, everyone is continually exposed to small amounts of formaldehyde, environmentally present in the air, our homes and endogenously in our own bodies.

1.3.3. Health problems from exposure to formaldehyde

Human studies have shown that chronic exposure to formaldehyde by inhalation is associated with respiratory symptoms, and eye, nose and throat irritation [31,69–71]. In the summer of 2007 it was first revealed that victims of Hurricane Katrina and Rita suffered health problems as a result of being housed in the 144,000 government-provided trailers containing dangerous levels of formaldehyde [72]. The Federal Emergency Management Agency (FEMA) received over 200 complaints from trailer residents suffering from respiratory problems and other symptoms due to exposure to formaldehyde, emitted from the materials used for constructing mobile homes [73]. For example, several trailers occupied by families comprised of pregnant mothers and young children had formaldehyde levels in their bedrooms reaching up to 1.2 ppm, resulting in sinus infections, burning sensation in the eyes, and general feeling of illness [42,73]. More recent measurements of 519 trailers between 21 December 2007 and 23 January 2008, by the Centers for Disease Control and Prevention (CDC), showed average levels of formaldehyde of about 0.077 ppm, with

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Table 2
Outdoor air concentrations of formaldehyde (FA) in various countries

Country	City	FA Concentration (ppb)	Sample Period	Reference
Australia	Melbourne	8.13[a]	N/A	Brown. (2002) [208]
	Brisbane	7.50	1992	NICNAS. (2006) [21]
Brazil	Rio de Janeiro	151.00	2002-2003	Martins, *et al*. (2007) [209]
Canada	Alert, Nunavut	0.40	1992	IPCS. (2002) [62]
	Toronto	0.65-7.30	1995	IPCS. (2002) [62]
Chile	Santiago city	3.90	2003	Rubio, *et al*. (2006) [210]
China	Beijing	15.86[a]	2005	Xu, *et al*. (2006) [211]
	Hong Kong	3.82-13.58[a]	2001	Ho, *et al*. (2006) [212]
	Maoming	10.57-13.82[a]	2003	Lin, *et al*. (2005) [213]
	Qingdao	2.96-8.09[a]	1997-1998	Tan, *et al*. (2002) [214]
Denmark	Lille Valby	1.20	1995	Christensen, *et al*. (2000) [63]
Egypt	Cairo	33.00	1999	Khoder, *et al*. (2000) [50]
Finland	Kuopio	35.00-55.00	1997-1998	Viskari, *et al*. (2000) [215]
Greece	Athens	8.70-13.98[a]	2000	Bakeas, *et al*. (2003) [216]
Italy	Rome	7.00-28.00	1994-1997	Possanzini, *et al*. (2002) [217]
Japan	Nagoya	4.72[a]	1998	Sakai, *et al*. (2004) [54]
	Shimizu	1.11-2.01[a]	2006	Ohura, *et al*. (2006) [53]
	Shizuoka	2.10[a]	2004	Kume, *et al*. (2007) [65]
Korea	Ansan	19.30	2004-2005	Pal, *et al*. (2007) [218]
	Ansan	28.20	N/A	Kim, *et al*. (2008) [219]
Lebanon	Beirut	4.50-4.60	2003-2004	Moussaa, *et al*. (2006) [220]
Mexico	Mexico City	5.90-110.00	1993	Báez, *et al*. (1995) [60]
	Mexico City	3.25-26.02[a]	1996-1998	Báez, *et al*. (2003) [61]
Portugal	Anadia	3.80	1996	Cerqueira, *et al*. (2003) [221]
	Tábua	5.20	1996	Cerqueira, *et al*. (2003) [221]
Sweden	Göteborg	3.09[a]	2000	Gustafson, *et al*. (2005) [49]
	Uppsala	1.06[a]	1998	Sakai, *et al*. (2004) [54]
Turkey	Izmir	5.93[a]	2003-2004	Seyfioglu,*et al*.(2006) [222]
UK	North London	3.40	1991–1992	Williams, *et al*. (1996) [223]
	West London	15.00	1991–1992	Williams, *et al*. (1996) [223]
USA	Baton Rouge, etc.[b]	1.50–7.40	1996-1997	Mohammed, *et al*. (2002) [224]
	Denver	2.30-3.92	1987-1991	Anderson, *et al*. (1996) [225]
	Houston	>7-30	2002	Chen, *et al*. (2004) [59]
	Los Angeles	3.17-3.58[a]	2000	Sax, *et al*. (2004) [55]
	New York	1.72-4.29[a]	1999	Kinney, *et al*. (2002) [51]

[a]Original data provided as mg/m^3 (1 ppb = 1.23 μg/m^3).
[b]Cities include: Baton Rouge, LA; Brownsville, TX; Brattleboro, VT; Burlington, VT; Camden, NJ; El Paso, TX; Garyville, LA; Galveston, TX; Hahnville, LA; Port Neches, TX; Rutland, VT; Underhill, VT; Winooski, VT.

some as high as 0.59 ppm [74]. Thus, FEMA aims to evacuate the remaining (approximately 38,000) trailers by the summer of 2008, before warm temperatures can promote an increased rate of formaldehyde release. Recently, FEMA adopted the NIOSH recommended 0.016 ppm (8 h TWA) [18] as their standard emission level for all future temporary housing units [75]. This level is recommended for occupational workers (usually adult males working ~8 h/day); however, it could remain a safety concern for some of the trailer tenants, such as children, pregnant women, the elderly and other sensitive groups who are continuously exposed to even longer durations than the former.

Other types of environmental exposures such as accidental spills have occurred in the past. In March of 1986, a railroad tanker car containing 190,000 lb of urea-formaldehyde resin spilled, releasing formaldehyde vapors into the environment around Crown Point, Alaska. The residents of Crown Point exhibited many symptoms of formaldehyde exposure such as nasal congestion, sore throats, headaches, coughs, conjunctivitis, fatigue, rashes, dizziness, diarrhea, shortness of breath, nausea and nosebleeds. Fifty percent still had recurrent, unresolved health complaints approximately 60 days following the spill [76].

The health effects of acute exposure to formaldehyde, like the Alaskan incident, are well documented while those of chronic exposure, like the Hurricane Katrina trailers, are less well known. Chronic, non-occupational exposure above the recommended occupational levels might be expected to lead to similar outcomes as those described in individuals exposed to formaldehyde in the workplace. If that were the case, symptoms underlying diseases with longer latency such as cancer would not be apparent in the short-term.

2. Formaldehyde as a human carcinogen and potential leukemogen

2.1. Formaldehyde is classified as a human carcinogen

Formaldehyde was long considered as a probable human carcinogen (Group 2A chemical) based on experimental animal

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studies and limited evidence of human carcinogenicity. However, the International Agency for Research on Cancer (IARC) reclassified formaldehyde as a human carcinogen (Group 1) in June 2004 based on "*sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans*". The sufficient evidence comes from six major cohort studies of industrial workers and seven case–control studies of nasopharyngeal cancer [77]. There was a statistically significant excess of deaths from nasopharyngeal cancer in the largest and most informative cohort study of industrial workers by the National Cancer Institute (NCI), with a strong exposure–response correlation between the cancer mortality rate and peak and cumulative exposures [78]. An excess of death from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest U.S. cohort of embalmers [79], and an excess of cases of nasopharyngeal cancer was observed in a Danish study of proportionate cancer incidence among workers at companies that manufactured or used formaldehyde [80]. Although some cohort studies reported fewer cases of nasopharyngeal cancer than expected [81–83], the deficits were small and the studies had low power to detect an effect on nasopharyngeal cancer. Of seven case–control studies of nasopharyngeal cancer [84–90], five found elevations of risk from exposure to formaldehyde. After a thorough discussion of the epidemiologic, experimental and other relevant data, the IARC panel concluded that formaldehyde is a carcinogen in humans. However, it should be noted that a few recent papers [91,92] have argued that the IARC conclusion was premature and that the largest and most influential NCI study should be re-evaluated.

In addition to the studies reviewed by IARC and included in the meta-analysis below, health risk assessments indicate that the estimated cancer risk from formaldehyde can be high. For example, a recent study reported that the estimated cancer risk of laboratory technicians and policemen was 20 and 1%, respectively, higher than the general population [93]. The excess cancer risk to laboratory technicians came mainly from formaldehyde exposure since ambient measurements showed that they were more highly exposed to formaldehyde as compared to the policemen who were more highly exposed to benzene [93], an established human leukemogen [94]. Further, the cancer potency values developed by the California EPA's OEHHA, expressed as estimated unit risk factors for benzene and formaldehyde are at 2.9E−5 and 6.0E−6 per $\mu g/m^3$, respectively [95]. However, the unit risk factors from Integrated Risk Information System (IRIS) database of the U.S. EPA show similar values for benzene and formaldehyde, 8.3E−6 and 1.3E−5 per $\mu g/m^3$, respectively [95,96].

2.2. Association of leukemia and occupational exposure to formaldehyde

The IARC reclassification of formaldehyde to Group 1 was based on the increased incidence and mortality rates of nasopharyngeal cancer [68,77]. However, these rates are very low in the U.S. population (0.7 and 0.2 per 100,000, respectively) [97], leading to relatively low predictions of the number of cancers caused annually by formaldehyde. Such predictions would change if formaldehyde were shown to cause more common and lethal cancers of greater prevalence. For example, lymphohematopoietic malignances, including leukemia (12.3 and 7.5 per 100,000) and lymphoma (22.0 and 8.1 per 100,000), occur at much higher incidence and mortality rates [97].

In their review, IARC also concluded that there was "*strong but not sufficient* evidence for a causal association between leukemia and occupational exposure to formaldehyde" [68,77]. The "*strong*" evidence for a causal relationship between formaldehyde exposure and leukemia comes from recent updates of two of the three major industrial cohort studies of formaldehyde-exposed workers [82,98]. These new data have strengthened a potential causal association between leukemia and occupational exposure to formaldehyde, especially for myeloid leukemia. Epidemiologists at the U.S. NCI have performed the largest of these cohort studies and demonstrated an increased relative risk (RR) of myeloid leukemia for workers with the highest levels of average exposure intensity (RR = 2.49; 95% confidence interval (CI), 1.03–6.03) and peak exposure (RR = 3.46; 95% CI, 1.27–9.43) compared to workers with lower exposures [98]. In contrast, the updated study of industrial workers in the United Kingdom did not find excess mortality from leukemia [81]. This study had sufficient size and reasonable power for detecting an excess of leukemia, but it did not report on peak exposures or the risk of myeloid leukemia specifically [77].

It should be noted that excess mortality from leukemia had been observed previously in studies of embalmers, funeral parlor workers, pathologists and anatomists exposed to formaldehyde [79,83,99–103]. These earlier studies received little attention, however, because of speculation that the results might be explained by possible contributions to the incidence of leukemia from other chemicals and perhaps viruses. But the recent IARC working group laid to rest the question of viral exposure when it concluded that there is little evidence that embalmers, pathologists, and the other occupations studied have a higher incidence of viral infections, or that viruses have a causal role in myeloid leukemia [77].

2.3. Controversy over the association due to limited biological plausibility

Some authors have argued that it is biologically implausible for formaldehyde to cause leukemia [104–109]. Their primary arguments against the human leukemogenicity of formaldehyde are: (1) it is unlikely to reach the bone marrow and cause toxicity due to its highly reactive nature; (2) there is no evidence that it can damage the stem and progenitor cells, the target cells for leukemogenesis; and (3) there is no credible experimental animal model for formaldehyde-induced leukemia. This led Pyatt et al. to recently comment that "*the notion that formaldehyde can cause any lymphohematopoietic malignancy is not supported with either epidemiologic data or current understanding of differing etiologies and risk factors for the various hematopoietic and lymphoproliferative malignancies*" [108]. Indeed, IARC itself concluded that "*based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans*" and stated that "*this is an area needing more research*" [68,77]. There is a need for scientists in public health, epidemiology and toxicology to generate new data on the question of biological plausibility and to work with national, international and regulatory agencies reviewing this controversial issue.

In this paper we review population studies published to date on formaldehyde-exposed workers and professionals, focusing on the incidence of and mortality from lymphohematopoietic malignances. Using the data obtained from the literature, we have performed a new meta-analysis to examine the association between exposure to high levels of formaldehyde and leukemia risk, particularly of the myeloid type. We then summarize the biological evidence for formaldehyde-induced hematotoxicity and genotoxicity with a primary focus on studies in the bone marrow and blood cells both *in vivo* and *in vitro*. Based on these reviews of existing data, we propose potential mechanisms for the observed association of formaldehyde with leukemia. Finally, we describe the need for new molecular epidemiological studies, which should provide the data necessary to critically evaluate our proposed mechanisms of leukemogenesis.

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3. Meta-analysis of formaldehyde and hematologic cancers in humans

3.1. Summary of previous meta-analyses and approach to the current review

Previous meta-analyses of leukemia and formaldehyde exposure have shown mixed results [91,110,111]. Blair et al. [110] first reported a summary relative risk (RR) of 1.6 for studies of professional workers with formaldehyde exposures and 1.1 for studies of industrial formaldehyde exposures. In a subsequent meta-analysis involving more recent studies, Collins and Lineker [111] reported a summary RR of 1.1 (95% CI, 1.0–1.2) for 18 studies of formaldehyde exposure or associated job titles, and thus concluded that the data did not provide consistent support for a relationship between formaldehyde exposure and leukemia risk. However, the study [111] did find an increased risk of leukemia in professional workers (embalmers, as well as pathologists and anatomists; RR = 1.6 and 1.4, respectively). In the most recent meta-analysis, Bosetti et al. reported summary relative risks of 0.90 (95% CI, 0.75–1.07) for formaldehyde-exposed industrial workers and 1.39 (95% CI, 1.15–1.68) for formaldehyde-exposed professional workers [91].

The meta-analysis reported here differs from the previous ones in several regards. The first major difference is that we focused our analyses on the *highest exposure* groups in each study. Several of the studies we included reported relative risks for different levels of exposure (e.g. tertiles of cumulative exposure). Simple cause and effect associations are best evaluated initially in groups with higher rather than lower exposures since relative risks are likely to be further away from 1.0 when exposures are high than when they are low. Higher relative risks are less likely to be subject to type II bias (i.e. inadequate study power) since all else being equal; study power is greater when relative risks are higher. Higher relative risks are also less likely to be due to confounding or other undetected bias [112]. For these reasons, we selected the *relative risk* for the highest exposure category from each study. In the previous meta-analyses, some of the individual relative risk estimates were for all exposure groups combined rather than for the most highly exposed group. If a true association exists, combining workers with very low exposures with workers with high exposures into one overall "exposed" group can dilute relative risk estimates towards the null.

Another difference between our meta-analysis and previous meta-analyses was that while others tended to select relative risk estimates for all types of leukemia combined, we selected relative risk estimates for *myeloid leukemia* when they were available. In fact, only six studies among all those reviewed indicated the specific types of lymphocytic and myeloid leukemia [79,82,83,98,102,103], and only four of them specified the subtypes of myeloid leukemia. Based on their original data (observed deaths), we have summarized the different subtypes of total and myeloid leukemia found in these studies in Table 3. It appears that myeloid leukemia (51%) is the primary type of leukemia observed with 19% being lymphocytic leukemia, while the others are unspecified. Furthermore, AML (64%, acute myeloid leukemia) is the major subtype of myeloid leukemia among leukemia deaths reported in formaldehyde-exposed individuals. Thus, we hypothesize that formaldehyde increases the risk of myeloid leukemia more than lymphocytic leukemia and causes predominantly AML. If this is true, then using relative risk estimates for all leukemias combined could also lead to relative risk estimates biased towards 1.0.

3.2. Selection of epidemiological studies collected from the literature

All epidemiologic studies on lymphohematopoietic cancer and formaldehyde exposure were identified from available databases including PubMed. The bibliographies of all relevant articles included in recent related review articles were also collected and cross-referenced. Only data published in peer-reviewed scientific journals or edited books were included. The current meta-analysis includes case–control and cohort studies ($n = 26$) [79,81–83,98–100,102,103,113–129] that provide relative risk estimates of hematological malignancies associated with occupations with known high formaldehyde exposures. Table 4 details the subsets of data from each study corresponding to each disease analyzed, including all types of hematological malignancy, all leukemia, myeloid leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM).

Although we analyzed several types of hematological malignancies, our primary hypotheses involved leukemia. Table 5 shows the included (top, light-shaded) and excluded (bottom, dark-shaded) studies and reasons for exclusion of our meta-analysis of leukemia. Studies of leukemia (or data therein) were excluded if: (1) they did not report estimates of variance (e.g. 95% CI) or include data needed to calculate them; (2) they had no cases of leukemia; (3) they included data pertaining to other leukemia subtypes as well as myeloid leukemia (in which case only myeloid data were used in the current meta-analysis); (4) they lacked relative risk estimates; (5) lacked a clearly exposed group; (6) reported data on the same cohort or group of subjects as another publication used in the meta-analysis (in which case only one publication was selected: either the one with the most appropriate exposure variable or the most recent one); (7) were not published in a scientific journal (such as a dissertation or an internal report, etc.); or (8) reported standardized proportionate incidence ratios (SPIR). With regard to use of SPIR, potentially, formaldehyde could

Table 3
Summary of formaldehyde exposure related leukemia and myeloid subtypes

	All Leukemia Deaths (n)				Myeloid Leukemia Deaths (n)			
References	Total	LL (%)[a]	ML (%)[a]	Other / US[b]	Total	AML (%)[a]	CML (%)[a]	Other / US[b]
Walrath and Fraumeni, 1983 [83]	12	4 (33)	7 (58)	1	7[c]	6 (86)		1
Walrath and Fraumeni, 1984 [103]	12	0 (0)	8 (67)	4	8[c]	6 (75)		2
Stroup *et al.*, 1986 [102]	10	1 (10)	6 (60)	3	6[c]	2 (33)	3 (50)	1
Pinkerton *et al.*, 2004 [82]	24	3 (13)	15 (63)	6	15	9 (60)	4 (27)	2[d]
Hauptmann *et al.*, 2003 [98]	69	19 (28)	30 (43)	20[d]				
Hayes *et al.*, 1990 [79]	51	7 (14)	24 (47)	20				
Total	178	34 (19)	90 (51)	54 (30)	36	23 (64)	7 (19)	6 (17)

[a]Indicating: lymphocytic leukemia (LL), myeloid leukemia (ML), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML).
[b]Unspecified (US).
[c]Data include acute monocytic leukemia (AML-M5), which was reported separately in the original studies.
[d]One less case was reported as other type in the original study.

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Table 4
Epidemiological (case–control and cohort) studies with data for hematological malignancies, which were included in the meta-analysis

Study (n)	All Types (19)	Leukemia (15)	Myeloid [a] (6)	HL[b] (8)	NHL[c] (11)	MM[d] (9)
Andjelkovich *et al.*, (1995) [113]	X	X		X	X	
Bertazzi *et al.*, (1989) [114]	X					
Blair *et al.*, (1993) [115]					X	
Boffetta *et al.*, (1989) [116]						X
Coggon *et al.*, (2003) [81]		X		X	X	X
Dell and Teta, (1995) [117]	X	X			X	X
Edling *et al.*, (1987) [118]						X
Hall *et al.*, (1991) [99]	X	X				
Harrington and Shannon, (1975) [119] [e]	X	X		X		
Hauptmann *et al.*, (2003) [98]	X	X	X	X	X	X
Hayes *et al.*, (1990) [79]	X	X	X	X	X	X
Heineman *et al.*, (1992) [120]						X
Levine *et al.*, (1984) [100]	X	X				
Liebling *et al.*, (1984) [121]	X					
Marsh *et al.*, (1996) [123]	X					
Marsh, (1982) [122]	X					
Pinkerton *et al.*, (2004) [82]		X	X	X	X	
Pottern *et al.*, (1992) [124]						X
Stayner, (1985) [125]	X					
Stellman *et al.*, (1998) [126]	X	X			X	X
Stern *et al.*, (1987) [127]	X	X				
Stone *et al.*, (2004) [128]	X					
Stroup *et al.*, (1986) [102]	X	X	X		X	
Walrath and Fraumeni, (1983) [83]	X	X	X	X	X	
Walrath and Fraumeni, (1984) [103]	X	X	X		X	
Wong, (1983) [129]	X	X		X		

[a] Indicating myeloid leukemia.
[b] Hodgkin lymphoma (HL).
[c] Non-Hodgkin lymphoma (NHL).
[d] Multiple myeloma (MM).
[e] Two RRs used in this analysis: one for lab technicians and another for pathologists.

increase the risks of cancers other than lymphohematopoietic cancer, and if so, using SPIR would bias relative risk estimates towards the null. The impact of excluding the study which reported SPIR [80] was assessed by performing sensitivity analyses with and without this study.

3.3. Methods applied in the new meta-analysis

The studies in our meta-analysis used many different metrics of exposure. For example, one study gave relative risks (RRs) for peak exposure [98], and others presented RRs for average exposure or cumulative exposure, while some studies presented RRs only for an "exposed" group defined solely by job title or work in a particular industry. Several studies gave RRs for more than one exposure metric (e.g. one RR for peak exposure and another RR for average exposure). For these studies, we selected only one RR to use in the meta-analysis in order to avoid counting data from the same group of subjects twice. When multiple RRs were given, we selected one in the following order: peak exposure, average exposure intensity, cumulative exposure, and exposure duration. Peak exposure (only from Hauptmann et al. [98]) was ranked first since metrics like average intensity and cumulative exposure may be less accurate measures of true exposure if workers with periods of very high exposure also have intervening time periods with little or no exposure. Several studies also reported relative risks for different levels of exposure (i.e. tertiles of high, medium and low exposure). As discussed above, because our focus was on evaluating causal inference rather than exact dose–response relationships, we selected the relative risk for the highest exposure category. In the analyses of leukemia, data specific for myeloid leukemia were used if available.

Summary relative risk estimates were calculated using both the fixed effects inverse variance weighting method [112] and the random effects method [130]. Heterogeneity among studies was assessed using the general variance-based method as described by Petitti [131]. An advantage of the random effects model over the fixed effects model is that it allows for the incorporation of between-study heterogeneity (if it is present) into the summary variance estimate and 95% confidence intervals. Some argue that this helps prevent the artificially narrow confidence intervals that may occur when the fixed effects model is used in the presence of between-study heterogeneity [131]. Some authors have suggested that because the random effects model incorporates between-study heterogeneity it is more conservative than the fixed effects model [131]. However, a problem with the random effects model is that study weighting is not directly proportional to study precision and greater relative weight is given to smaller studies. This can potentially lead to summary results that are actually less conservative than in the fixed effects model [132]. To avoid these problems, we used the method presented by Shore et al. [133] and used in several subsequent meta-analyses [134–137]. In Shore's method, the summary relative risk estimate itself is calculated by directly weighing individual studies by their precision as in the fixed effects model while between-study heterogeneity is only incorporated into the calculations of the summary relative risk's variance (i.e. the 95% CI) [133].

Publication bias was assessed using funnel plots and Egger's and Begg's tests [138,139]. The funnel plot is a graphical

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Table 5
Comparison of recent meta-analyses on formaldehyde and leukemia

	Current meta-analysis			Bosetti et al., 2008 [91]			Collins and Lineker, 2004 [111]		
Study	**RR** [a]	**N** [a]	**Group**	**Comparison**	**RR**	**N**	**Comparison**	**RR**	**N**
Andielkovich et al., 1995 [113]	0.43	2	Formaldehyde exposed	Same [b]			Same [b]		
Coggon et al., 2003 [81]	0.71	8	Average exposure > 2 ppm	Total cohort	0.91	31	Total cohort	0.91	31
Dell and Teta, 1995 [117]	2.65	8	R and D workers	Not used			Dell, 1993 dissertation	0	0
Hall et al., 1991 [99]	1.52	4	All cohort	Same [b]			Same [b]		
Harrington and Shannon, 1975 [119] [c]	0.45	1	Lab technicians	Same [b]			Not used		
	0.62	1	Pathologists	Same [b]			England only	0.77	1
Hauptmann et al., 2003 [98]	3.46	14	Myeloid, peak exposure ≥ 4 ppm	All cohort & leukemias	0.85	65	All cohort & leukemias	0.85	65
Hayes et al., 1990 [79]	1.57	24	Myeloid	Same [b], & lymphocytic leukemia	0.74	7	All leukemias	1.52	51
Levine et al., 1984 [100]	1.6	4	All cohort	Same [b]			Same [b]		
Pinkerton et al., 2004 [82]	2.19	8	Myeloid, duration 10+ yrs	All cohort & leukemias	1.09	24	All cohort & leukemias	1.09	24
Stellman et al., 1998 [126]	0.96	12	Formaldehyde exposed	Not used			Not used		
Stern et al., 1987 [127]	1.7	6	Tannery, duration 10+ yrs	Not used			Not used		
Stroup et al., 1986 [102]	8.8	3	Myeloid (CML only)	All leukemias	1.5	10	All leukemias	1.5	10
Walrath and Fraumeni, 1983 [83]	1.46	6	All reported myeloid	All leukemias	1.40	12	All leukemias	1.4	12
Walrath and Fraumeni, 1984 [103]	1.50	6	All reported myeloid	All leukemias	1.75	12	Unknown	2.67	4
Wong, 1983 [129]	1.35	2	Employed < 1960	Not used			Not used		
Band et al., 1997 [140]			Not used, criterion 5 [d]	Not used			Not used		
Edling et al., 1987 [118]			Not used, criteria 2 and 4 [d]	Not used			Estimated E [a]	0	0
Hansen and Olsen, 1995 [80]			Not used, criterion 8 [d]	Not used			Used	0.83	39
Harrington and Oakes, 1984 [226]			Not used, criterion 6 [d]	Not used			Used	1.67	2
Linos et al., 1980 [141]			Not used, criteria 4 and 5 [d]	Not used			Unknown	2.1	4
Matanoski, 1991 [142]			Not used, criterion 7 [d]	Used	1.35	31	Used	1.35	31
Ott et al., 1980 [143]			Not used, criterion 1 [d]	Not used			Estimated E [a]	2.5	3

[a] Relative Risk (RR), calculated as the ratio of the number of cases observed (N) to the number of expected cases (E).
[b] Same means the same RR used as in the current meta-analysis;
[c] Two RRs used in this analysis: one for lab technicians and another for pathologists;
[d] Criteria for exclusion: 1) No confidence-intervals (CI); 2) No leukemia cases; 3) Relative risk (RR) on non-myeloid leukemia not used; 4) No RR estimate; 5) No clear exposed group; 6) Overlap with another study; 7) Not published in a scientific journal; and, 8) Standardized proportionate incidence ratios reported.

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Table 6
Results of the meta-analysis of formaldehyde and lymphohematopoietic cancer

		Fixed Effects Model[b]			Shore Adjustment		Random Effects Model			Heterogeneity[c]	
Outcome	N[a]	RR	CI_L	CI_U	CI_L	CI_U	RR	CI_L	CI_U	X^2	*p*
All types combined	19[d]	1.25	1.12	1.39	1.09	1.43	1.21	1.03	1.42	30.50	0.05
All leukemia	15[d]	1.54	1.24	1.91	1.18	2.00	1.57	1.17	2.11	21.93	0.11
Myeloid leukemia	6	1.90	1.41	2.55	1.31	2.76	2.08	1.37	3.16	8.04	0.15
Hodgkin lymphoma	8	1.23	0.67	2.29	--	--	--	--	--	6.11	0.53
Non-Hodgkin lymphoma	11	1.08	0.86	1.35	--	--	--	--	--	3.24	0.98
Multiple myeloma	9	1.31	1.02	1.67	--	--	--	--	--	5.49	0.70

[a]Number of studies.
[b]Fixed effects RR (relative risk) and CI (confidence interval) used unless heterogeneity is present, then the random effects or Shore numbers are presented.
[c]Heterogeneity defined as present when χ^2 > degrees of freedom (d.f. = number of studies minus 1).
[d]Two RRs are used in the analysis of Harrington and Shannon [119]: one for lab technicians and another for pathologists.

presentation of each study's effect size (the log of the relative risk in our case) versus an estimate of its precision (usually the standard error (S.E.) of the log of the relative risk). In the absence of publication bias, studies should be symmetrically distributed around the summary estimate of effect size. This plot should appear in a funnel shape because the scattering of effect sizes should decrease as the precision of the studies increases. If there is bias against publication of smaller studies with null or unexpected results, the funnel shape will appear asymmetrical.

3.4. Results from the current meta-analysis

Table 6 shows the results of the meta-analysis. As discussed above, the fixed effects model is used to calculate relative risk estimates and confidence intervals unless heterogeneity is present. If heterogeneity is present (defined as the χ^2-test statistic for heterogeneity being greater than the degrees of freedom which equals the number of studies minus one), calculations using the random effects or Shore method are applied. Using data from 19 studies (listed in Table 4), the summary relative risk (RR) for all types of lymphohematopoietic cancer combined was 1.25 (95% CI, 1.09–1.43, Shore adjusted). The summary relative risk was elevated in the 15 studies (listed in Table 4) reporting data on all leukemia (RR = 1.54; 95% CI, 1.18–2.00, $p < 0.001$, Shore adjusted) with the highest summary relative risk seen in the six studies of myeloid leukemia (RR = 1.90; 95% CI, 1.31–2.76, $p = 0.001$, Shore adjusted). All six studies of myeloid leukemia had relative risks of 1.4 or higher [79,82,83,98,102,103].

In the Stroup et al. study [102], specific data on myeloid leukemia classification were only available for the period between 1969 and 1979. If we used the Stroup et al. RR for all leukemia types combined for the entire study period instead of the RR for just myeloid leukemia (3 CML of 6 ML), our meta-analysis summary RR for all leukemia (1.47, 95% CI, 1.19–1.81) decreases slightly. Removing the Stroup et al. myeloid RR from the myeloid meta-analysis causes only a small decrease in our myeloid summary RR (1.75, 95% CI, 1.30–2.37, $n = 5$). A Forest plot of studies of formaldehyde and leukemia is shown in Fig. 2. Eleven of the 15 studies reported relative risks above 1.0. No evidence of publication bias was seen in the analysis of leukemia in the funnel plot (Fig. 3) or in Eggers ($p = 0.99$) or Beggs ($p = 0.75$) tests.

As described above, peak exposure was used only in one study [98]. Using the relative risk for the highest category of average exposure intensity in this study, instead of that for peak exposure, had a minimal impact on the meta-analysis. The summary relative risk in the all-leukemia analysis changed from 1.54 (95% CI, 1.18–2.00) to 1.52 (95% CI, 1.18–1.96), a negligible difference. Two studies (Band et al. [140] and Hansen and Olsen [80]) were excluded from the "All leukemia" analysis (Table 6) because some pulp paper workers did not have apparent formaldehyde exposure [140] and SPIRs instead of RRs were used [80] (see Table 5). Inclusion of the study by Band et al. into the analysis of "All

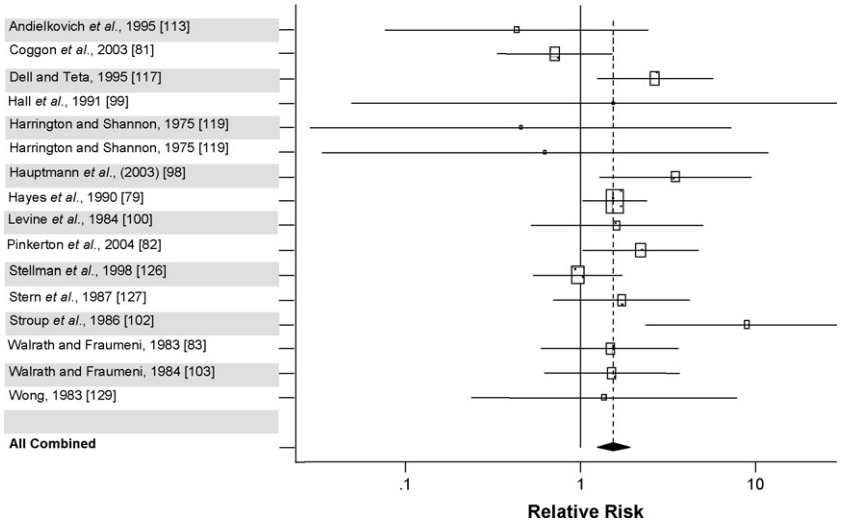

Fig. 2. Relative risks of leukemia in occupational and professional workers exposed to formaldehyde from the studies in the current meta-analysis presented as a Forest plot.

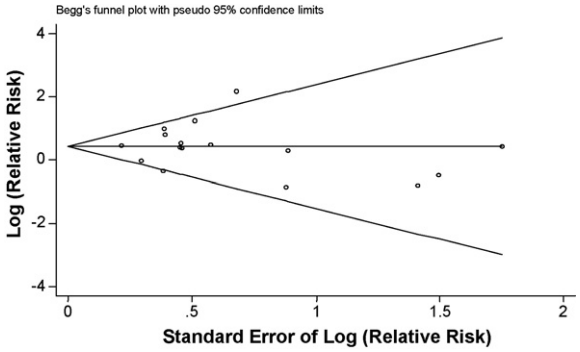

Fig. 3. Funnel plot comparing the logarithm of each study's relative risk and standard error for studies included in the meta-analysis of formaldehyde and leukemia. The funnel plot is a graphical presentation of each study's effect size (log RR) versus an estimate of its precision (the S.E. of the log RR). The funnel shape suggests a lack of publication bias arising from the meta-analysis.

leukemia'' led to a decrease in the relative risk of leukemia from 1.54 to 1.24 (95% CI, 0.97–1.59, $p = 0.04$), while including the Hansen and Olsen study slightly decreased the ''All leukemia'' relative risk from 1.54 to 1.41 (1.10–1.79, $p = 0.003$). The summary relative risk (Table 6) was not clearly elevated in the Hodgkin (RR = 1.23; 95% CI, 0.67–2.29) and non-Hodgkin (RR = 1.08; 95% CI, 0.86–1.35) lymphoma studies, but was modestly increased in the nine studies of multiple myeloma (RR = 1.31; 95% CI, 1.02–1.67, $p = 0.02$).

Overall, the results of our meta-analysis suggest that formaldehyde causes leukemia, specifically myeloid leukemia. As discussed earlier, two other recent meta-analyses have produced mixed results [91,111]. A comparison of our meta-analysis with these two previous studies is shown in Table 5. In general we found evidence of a stronger association between formaldehyde and leukemia than these previous meta-analyses. The primary reason for this is the different results used from the studies by Hauptmann et al. [98], Stroup et al. [102] and Pinkerton et al. [82]. For these studies, we used relative risks for myeloid leukemia and/or for the highest exposure category in each study. In the two previous meta-analyses [91,111], relative risks for all exposure groups combined and all leukemia types combined were used. If we replace the results we used for these three studies with the results used in the previous meta-analyses the summary relative risk we identified for leukemia drops from 1.54 (95% CI, 1.18–2.00) to 1.10 (95% CI, 0.93–1.31). The previous meta-analyses also used several studies that we do not. These studies and the reasons for excluding them from the current analysis are described above and are listed in Table 5. Exclusion of these studies had only a relatively small impact on our summary relative risks for leukemia. If we add the five studies [80,118,141–143] used by the previous meta-analyses, but not used by us, the summary relative risk for leukemia falls slightly but remains statistically significant (RR = 1.38; 95% CI, 1.15–1.65; $p < 0.001$).

In summary, by applying our methodology of selecting data on the most highly exposed groups from each study when available, utilizing relative risks and examining myeloid leukemia separately (when data were available), our new meta-analysis provides evidence of an association between formaldehyde exposure and human leukemia, especially for myeloid leukemia.

4. Formaldehyde-induced hematotoxicity and genotoxicity

Most chemically induced human leukemias are acute myeloid leukemia (AML) and precursor myelodysplastic syndromes (MDS). Leukemia arises through damage to early stem or progenitor cells in the bone marrow (detailed in next section). Such damage to the bone marrow often manifests itself as hematotoxicity and/or genotoxicity, both of which occur following exposure to chemicals that cause leukemia. Established chemical leukemogens, such as chemotherapeutic drugs (alkylating agents and topoisomerase II inhibitors) and benzene, are capable of inducing toxicity to the blood forming system (hematotoxicity) and damaging DNA and/or chromosomes (genotoxicity). For example, exposure to benzene (even at relatively low doses) induces lowered blood cell counts and increased chromosome alterations [94,144–149].

4.1. Formaldehyde-induced hematotoxicity

The published data on formaldehyde hematotoxicity are limited and inconsistent. Several previous studies showed that formaldehyde altered the counts of different types of blood cells. One study reported that exposure to formaldehyde in humans reduced white blood cell counts [150]. Another recent study concluded that formaldehyde increased B cells, but decreased total T cells (CD3) and T-helper cells (CD8) in the blood of exposed workers, while T-suppressor (CD4) cells remained unchanged [151]. However, a study of people environmentally exposed to formaldehyde during an accidental spill showed no difference in white blood cells, lymphocytes, or T-cells (CD4 and CD8) [76]. In male rats exposed to a high dose of formaldehyde, increased monocytes, red blood cells and hemoglobin were detected, but lymphocyte counts were decreased [152]. The inconsistencies and limitations in the published studies suggest that more comprehensive studies of the hematological effects of formaldehyde in exposed populations are needed.

4.2. Formaldehyde-induced genotoxicity

Formaldehyde is genotoxic and induces both DNA damage and chromosome changes, frequently expressed as DNA–protein crosslinks (DPCs), chromosomal aberrations (CA), sister chromatid exchanges (SCEs), and micronuclei (MN). A large number of studies have demonstrated that these alterations can be induced by formaldehyde in cell culture experiments and *in vivo* in humans and experimental animals at the sites of formaldehyde exposure [19,68]. Other studies have shown that these changes can occur in the lymphocytes of exposed people although the results of these studies are more variable, with increases in damage being reported in some studies and not in others [19,68]. In recent years and after the literature was compiled for the earlier reviews, there have been a number of studies reporting that formaldehyde can induce damage in circulating lymphocytes [151,153–155]. In light of these new reports and the fact that the focus of this review is on mechanisms that could contribute to formaldehyde-induced leukemia, we have chosen to highlight examples of positive studies with an emphasis on those that have detected damage in the cells of the blood or bone marrow of humans and experimental animals. While discrepant results are found in the literature, the number of studies reporting positive results indicates that formaldehyde is able to cause a range of genotoxic effects in the DNA and chromosomes of lymphocytes, and possibly other bone marrow-derived cells. Additional details and examples are provided in the following sections.

4.2.1. DNA–protein crosslinks

Formaldehyde is thought to produce its genotoxic effects primarily through the induction of DPCs. The covalent crosslinking of proteins to DNA, defined as DPCs, is induced by a variety of endogenous and exogenous agents including metals and formaldehyde [156]. A schematic of the formaldehyde-induced cross-

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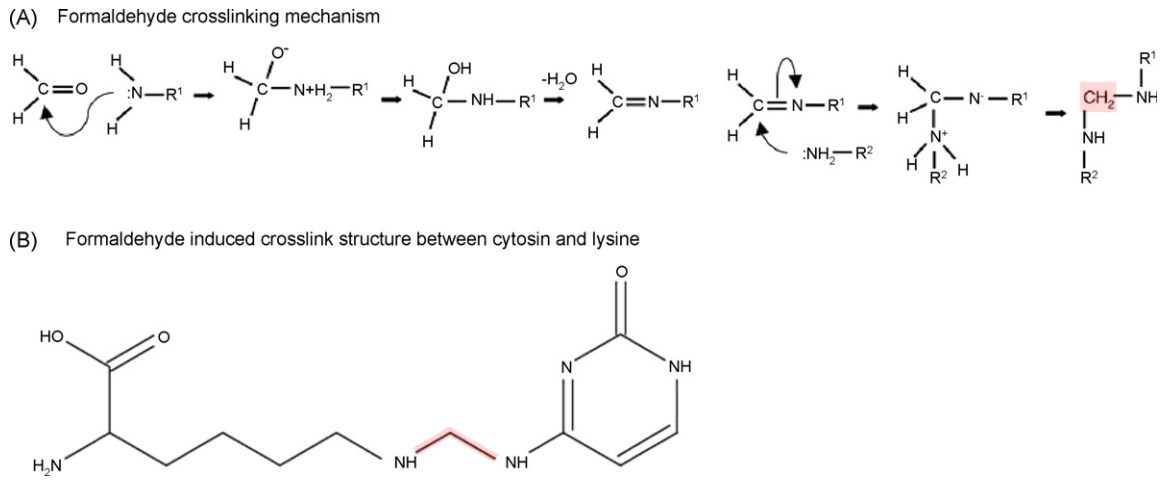

Fig. 4. A schematic mechanism (A) and a representative structure (B) of formaldehyde-induced DNA–protein crosslinks [156]. (A) Formaldehyde crosslinking mechanism depicting the steps in the reaction of formaldehyde with an amino group (of a protein side chain) to form a Schiff base (in step 1) which can then go on and react with another amino group (of a DNA base) to complete the crosslink. (B) Crosslink structure showing a formaldehyde-induced crosslink between cytosine and lysine.

linking mechanism and the resulting DPC structure are shown in Fig. 4. The induced DPCs have the following general structure: histone-containing lysine–NH–CH_2–NH–DNA (Fig. 4) and are the major mechanism for formaldehyde's induction of DNA lesions [157]. Formaldehyde-induced DPCs have been detected in the nasal mucosa of exposed animals [158–161] and in human lymphocytes [162–164] and V79 Chinese hamster lung cells exposed *in vitro* [165]. It was recently shown that cells lacking the FANC/BRCA DNA damage repair pathway are hypersensitive to formaldehyde and that this pathway is essential to counteract formaldehyde-induced DPCs [166]. Because DPCs are longer-lived than most DNA adducts, and are only slowly or partially repaired, the DPC level could serve as a biomarker of internal formaldehyde dose. The level of DPCs has been used as a biomarker of formaldehyde exposure in mammalian cells [159,167], and has also been correlated with formaldehyde-induced carcinogenesis in animals [96,161].

In the only human studies performed to date by Shaham et al. [164,168], elevated DPCs were detected in the peripheral mononuclear cells of formaldehyde-exposed workers. These findings have been questioned, however, because of the excessively high level of DPCs reported in the controls, which are an order of magnitude higher than those typically reported [169]. Therefore, Shaham et al.'s findings need to be replicated in other molecular epidemiology studies.

Formaldehyde induces DPCs in V79 Chinese hamster cells in a manner that correlates with increased cytotoxicity and clastogenicity [165]. They are expected to act as bulky helix-distorting adducts, and are likely to physically block DNA replication and transcription, and to eventually interrupt the DNA metabolic machinery by anchoring the chromatin and preventing its remodeling [156]. In addition, the biologically relevant proteins involved in formaldehyde-induced DPCs are major histones (H1, H2A, H2B, H3 and H4) [170] and vimentin [171]. Thus, formaldehyde-induced DPCs have the potential to cause (or correlate with) the increased levels of chromosomal damage in exposed individuals, but this needs to be further substantiated. In addition, the correlation between chemically induced DPCs and cancer risk is less clear. One case–control study showed that DPC frequencies detected in the blood lymphocytes of breast cancer patients was significantly higher than in control subjects, which may indicate an association of DPCs with increased breast cancer risk, but may also be simply a consequence of the disease [172]. Prospective studies are needed to further evaluate this association.

4.2.2. Cytogenetic alterations

Increased levels of cytogenetic alterations (CA, SCEs, MN) have been reported to occur in the bone marrow of exposed mice and rats [173,174] and in mammalian cells *in vitro* such as Syrian hamster embryo cells [175] following exposure to formaldehyde. Several studies have found increased CA in human peripheral blood lymphocytes obtained from individuals occupationally exposed to formaldehyde as compared to their respective controls [176–178]. The effects were particularly strong for the relationship between formaldehyde exposure and structural aberrations, such as chromosome breaks [179,180], dicentrics and ring chromosomes [181]. However, these studies have a number of methodological weaknesses, including poor exposure assessment, non-current measurement of exposure and outcome, small sample size, etc. There is a need to replicate these findings in better-designed studies. Formaldehyde has also been reported to induce SCEs and MN in the circulating lymphocytes of exposed individuals [151,153–155,182,183]. Overall, these studies provide substantial evidence that formaldehyde can damage chromosomes.

Chromosomal aberrations (CA) [184,185], and more recently MN [186] (but not SCE), have been shown to be predictive of overall future cancer risk, especially for hematological malignancies [187]. It should be noted that these traditional cytogenetic assays (CA, SCEs and MN) are unable to detect leukemia-specific chromosomal aberrations (such as monosomy 7, trisomy 8, and translocations, etc.) known to be on the causal pathways to leukemia and therefore even better biomarkers of the disease [94,188]. Modern molecular cytogenetic assays such as fluorescence *in situ* hybridization (FISH) can be readily applied to the detection of these specific chromosomal changes. To date, however, formaldehyde has not been demonstrated to induce leukemia-specific chromosomal aberrations. Studies demonstrating the presence of these specific chromosomal changes in any cell type but particularly in hematopoietic progenitor cells, the target cells of importance in leukemia, would strengthen the biological plausibility.

5. Potential mechanisms of formaldehyde-induced leukemia

Leukemias and related disorders originate in pluripotent precursor cells located in the bone marrow that normally give rise to all blood cells [189,190]. Disruptions of the normal hierarchy of maturation result in hematological disorders characterized by either excesses or deficiencies of mature effector cells

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[191,192]. The disorders of myeloid origin include acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and myeloproliferative disorders such as chronic myeloid leukemia (CML). Hematological disorders of lymphoid origin include acute lymphocytic leukemia (ALL), chronic lymphocytic leukemias (CLL), lymphoma (HL and NHL) and multiple myeloma (MM), which arise from stem cells in the bone marrow (ALL) or from more mature cells outside of the bone marrow (CLL, lymphoma, and myeloma), possibly in the lymph nodes and/or germinal centers [193,194].

For a hematopoietic stem or progenitor cell to become malignant, it must acquire genetic mutations and develop genomic instability. There are a number of factors that predispose cells to this genomic instability [195,196]. These include error prone DNA repair, imbalance in the nucleotide precursor pool, generation of reactive oxygen species, and exposure to genotoxic xenobiotic agents (chemotherapeutic drugs and benzene) delivered to the bone marrow, which can cause AML and MDS. Of course, the majority of patients treated with these cancer drugs and workers exposed to benzene do not go on to develop AML/MDS, as there are a number of factors, which have evolved to prevent DNA instability, including maintenance of the primary DNA sequence by base selection, proof reading and mismatch correction. In addition, depending on the extent of the damage incurred, well defined DNA repair pathways can repair a range of damage at cell cycle checkpoints, or induce apoptosis [197–199]. However, mutagenic damage sustained by target cells with un-repaired damage that fail to undergo apoptosis may initiate leukemogenesis.

5.1. Overview of the mechanisms of formaldehyde-induced leukemia

As described above, leukemia originates in the pluripotent stem and progenitor cells that are mainly located in the bone marrow [200]. A portion of the bone marrow stem and progenitor cells circulate in the peripheral blood where they constitute up to 0.05% of circulating nucleated cells [189,201]. These cells return to the bone marrow, and, therefore, peripheral blood represents another possible target site of formaldehyde-induced leukemogenesis. It is commonly postulated that most inhaled airborne formaldehyde is detoxified upon contact with mucosal surfaces of the mouth and nose, and that little or no formaldehyde reaches the internal organs, such as bone marrow. However, it seems plausible that formaldehyde could produce damage to the target hematopoietic stem cells via the three possible mechanisms described below and illustrated in Fig. 5: (a) by damaging stem cells in the bone marrow directly, as most other leukemogens do; (b) by damaging hematopoietic stem/progenitor cells circulating in the peripheral blood; and (c) by damaging the primitive pluripotent stem cells present within the nasal turbinates and/or olfactory mucosa. In the latter two models, damaged stem/progenitor cells would then travel to the bone marrow and become initiated leukemic stem cells.

5.1.1. Targeting bone marrow hematopoietic stem cells (traditional model)

Similar to other chemical leukemogens [202], formaldehyde could potentially damage stem cells in the bone marrow directly (Fig. 5a). In this traditional model, formaldehyde is absorbed during respiration, and travels through the blood to the bone marrow where it exerts its toxic and mutagenic effects. This model has been considered unlikely as formaldehyde is not thought to reach bone marrow in significant quantities and there has been a general lack of overt bone marrow toxicity in experimental animals [173,174]. However, the chemistry of formaldehyde is complex. It exists as a gas at room temperature but in the presence

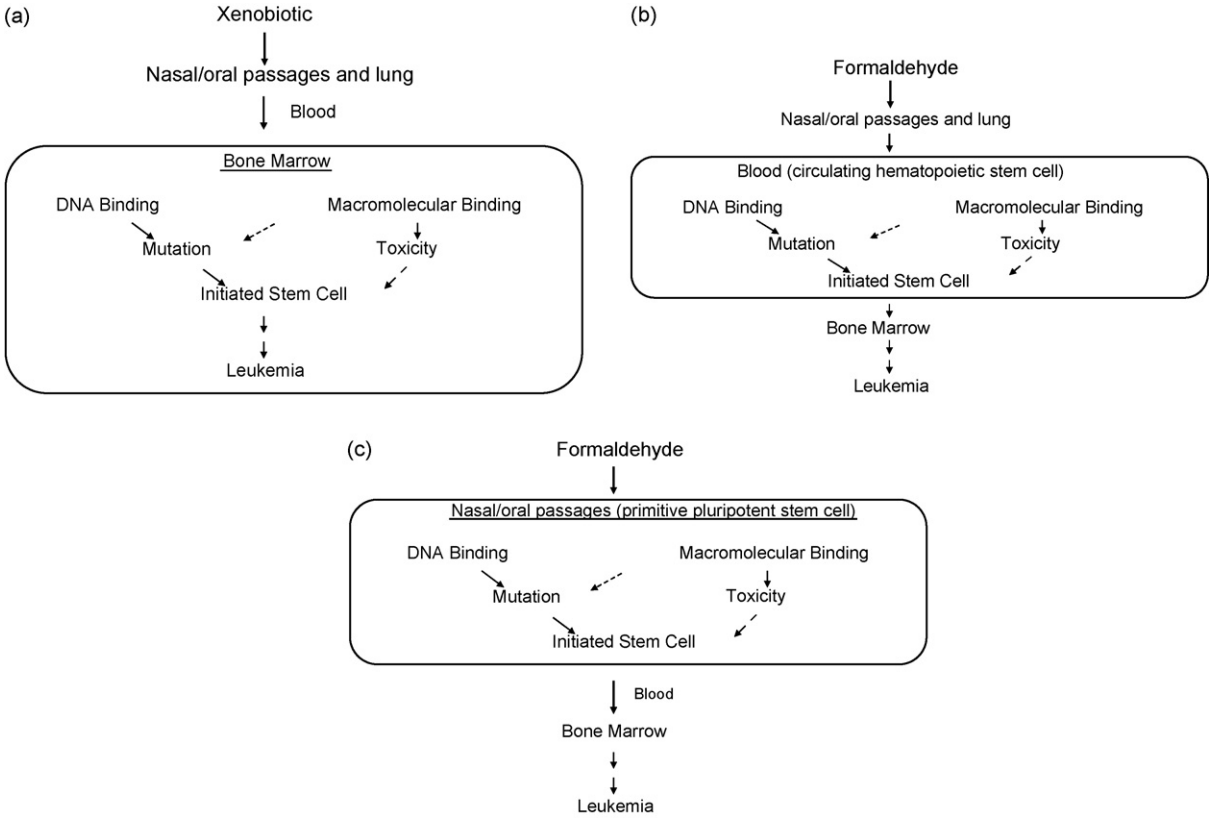

Fig. 5. Potential models to illustrate how formaldehyde can damage stem cells. (a) Traditional model: targeting hematopoietic stem cells in bone marrow directly; (b) alternate model 1: targeting stem and progenitor cells in circulating peripheral blood; and (c) alternate model 2: targeting primitive pluripotent cells in nasal/oral passages.

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of water it dissolves and converts mostly to its hydrate methanediol [$CH_2(OH)_2$], in which form it exists in equilibrium with formaldehyde (CH_2O) and thus could potentially reach the bone marrow [203,204]. Formaldehyde is however difficult to measure in the tissues and reacts rapidly with glutathione. Further, it is a substrate for one-carbon metabolism and can be rapidly incorporated into macromolecules throughout the body, making its toxicokinetic fate hard to study [203]. Thus, transport of reactive formaldehyde (as methanediol) to the marrow cannot be ruled out and is, in fact, entirely plausible; therefore one can hypothesize that formaldehyde may cause leukemia by directly inducing DNA damage and chromosome aberrations in hematopoietic stem or early progenitor cells in the bone marrow, promoting their development into leukemic stem cells.

We have postulated two alternate models (described below) based on a mechanism involving circulating stem cells, to explain how formaldehyde might induce leukemia if it were not able to reach bone marrow in sufficient qualities to damage stem cells directly.

5.1.2. Targeting blood stem cells and progenitors (alternate model 1)

The second model (Fig. 5b) by which formaldehyde might cause leukemia in humans proposes that after formaldehyde reaches the nasal/oral passages and lung, it crosses into the blood and induces mutations or pre-mutagenic lesions in circulating hematopoietic stem cells. The mechanism by which this could occur is uncertain, but we hypothesize that the critical DNA or macromolecular binding occurs in the blood. When the affected cells proliferate, un-repaired lesions could lead to leukemogenic mutations and cellular toxicity. The initiated stem cell would then be re-incorporated into the bone marrow, eventually leading to leukemia.

There are several lines of evidence that indicate that this mechanism is plausible. The detection of DNA–protein crosslinks and cytogenetic damage in the lymphocytes of exposed workers indicates that formaldehyde is able to reach cells of the peripheral blood in a reactive form and cause genetic lesions in DNA and chromosomes [68,176–178,182,205]. The same types of damage that occur in the peripheral lymphocytes would also be expected to occur in circulating hematopoietic stem cells. Upon their return and proliferation within the bone marrow, pre-mutagenic lesions within these altered stem cells would be converted into mutagenic lesions. Mutations affecting critical leukemia-related genes would represent a key initial step in the conversion of a hematopoietic stem cell into a leukemic stem cell [195,196].

5.1.3. Targeting pluripotent nasal/oral stem cells (alternate model 2)

The third model proposes that formaldehyde directly induces mutations or pre-mutagenic lesions in primitive pluripotent stem cells, which reside in the oral or nasal passages (Fig. 5c). Either through normal trafficking or trafficking enhanced by formaldehyde-induced cytotoxicity, the damaged stem cells are released from the nasal passages, circulate through the blood, and are eventually incorporated into the bone marrow where they could potentially induce leukemia. The plausibility of this model is bolstered by several lines of evidence. It has been well established that formaldehyde can induce toxicity and DNA–protein cross links in the nasal passages of laboratory animals including non-human primates (reviewed in [68]). Similar lesions could almost certainly occur in humans, and reports of increased micronuclei in the nasal and oral mucosa of exposed humans establish that damage can occur at sites of formaldehyde exposure (reviewed in [68]). During normal cell proliferation or more likely during proliferation that occurs secondary to formaldehyde cytotoxicity, DNA damage and lesions occurring in primitive pluripotent stem cells located in the olfactory mucosa could be converted into mutations. These mutated stem cells would then migrate to the bone marrow either during normal trafficking or trafficking enhanced by cytotoxicity in the mucosa. Alternatively, pluripotent olfactory stem cells containing pre-mutagenic lesions could migrate to the bone marrow where, upon replication, the pre-mutagenic lesions would be converted into mutations. As indicated above, mutations occurring in key leukemia-related genes would represent an initial step in the conversion to a leukemic stem cell [195,196].

This postulated mechanism is supported by a recent study showing that olfactory epithelial cells obtained from rat nasal passages were capable of re-populating the hematopoietic tissues of irradiated rats and gave rise to hematopoietic stem/progenitor cells ($CD34^+$) of multiple lineages *in vivo* including myeloid and lymphoid cells [206]. The presence within the nasal passages of stem cells capable of generating multiple hematopoietic cell lineages provides a critical piece of evidence to support the plausibility of this third proposed model.

Given the likely dynamics of stem cell turnover between the nasal/oral passages, blood and bone marrow, particularly in the context of continuous high formaldehyde exposure (such as occupational exposure), one can imagine the targeting of sufficient stem cells through these two alternative models to induce leukemia, which would arise from a single mutated cell, be clonal in nature, and, have a protracted latency.

5.2. Detection of damage to hematopoietic stem and progenitor cells

We have hypothesized that formaldehyde could cause leukemia by directly inducing DNA damage and chromosome aberrations in hematopoietic stem or early progenitor cells in the bone marrow, or those circulating in the blood, thereby promoting their development into leukemic stem cells. It is possible to measure formaldehyde-induced damage in circulating myeloid progenitor cells because these cells can be harvested and cultured in colony-forming assays using growth factor-enriched semi-solid media [207]. During the 12–14 days of culture, the progenitor cells establish individual colonies while terminally differentiated cells such as lymphocytes and granulocytes die out. The individual colonies can then be classified microscopically according to the progenitor cell type. Colonies arising from the most primitive, early progenitor cells are called colony-forming-unit–granulocyte, erythroid, monocyte, macrophage, megakaryocyte (CFU-GEMM) because these progenitors can give rise to any of these cell types. Colonies derived from more committed progenitor cells that give rise to reticulocytes and erythrocytes are called burst-forming unit-erythroid (BFU-E), whereas those that give rise to granulocytes and macrophages are called colony-forming unit–granulocyte-macrophage (CFU-GM).

We recently applied these colony assays in a study of Chinese workers exposed to varying levels of benzene, a known myeloid leukemogen, and reported a dose-dependent decrease in the number of these colony formations [145]. We also found that benzene caused a greater proportional decrease in colony formation than in levels of mature granulocytes, suggesting that early myeloid progenitor cells are the targets for the hematotoxic effects of benzene in humans. No studies to date have examined the effects of formaldehyde on colony formation from hematopoietic stem and/or progenitor cells, but could be performed in formaldehyde-exposed workers. Such studies could help to bridge the gap between the epidemiological evidence of leukemia, lymphomas, and myeloma due to formaldehyde exposure and our current understanding of possible mechanistic routes for the induction of these lymphohematopoietic malignancies.

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6. Conclusions and future directions

In this review we have performed a comparative global survey of formaldehyde occupational and environmental exposure limits. We concluded that: (1) the U.S. OEL (0.75 ppm, 8h TWA, OSHA PEL) has remained at the same high level since 1992, in comparison to other countries who have lowered their OELs; (2) the U.S. has no regulation for non-occupational indoor formaldehyde exposure limits, while other developed and developing nations have established such standards, according to the recommendations from WHO (0.08 ppm); and (3) unlike the jurisdictions of Japan and California, the U.S. has not yet established a national reference exposure level for atmospheric formaldehyde.

Additionally, we describe the epidemiological and biological evidence that appears to support an association between formaldehyde and leukemia. In particular, a number of epidemiological studies document a significant association between occupational exposure to formaldehyde and excess mortality from leukemia. A new meta-analysis of these published studies provides evidence of an association with leukemia, particularly of the myeloid type. However, the question of biological plausibility remains and requires further investigation.

We note that formaldehyde causes chromosomal aberrations and DNA–protein crosslinks, both of which could potentially cause the mutations required for the development of leukemia if they occurred in the target cells for leukemogenesis. We hypothesize that formaldehyde may cause leukemia by directly inducing DNA damage and chromosome aberrations in hematopoietic stem or early progenitor cells in the bone marrow, promoting their development into leukemic stem cells. We also propose two alternate mechanisms by which formaldehyde might induce leukemogenesis by damaging the hematopoietic stem and progenitor cells circulating in the blood or the pluripotent stem cells located in the nasal passages.

In future studies, researchers could explore whether formaldehyde is able to cause leukemia-initiating events in the critical target cells for myeloid leukemogenesis. Specifically, it should be determined if formaldehyde can induce leukemia-specific chromosomal aberrations and DNA–protein crosslinks in myeloid progenitor cells, both *in vivo* in exposed workers and *in vitro* in cultured human cells. Such studies would compliment ongoing epidemiological studies further examining the association with leukemia, and would increase our understanding of the potential mechanisms by which formaldehyde may induce myeloid leukemia in humans.

Conflict of interest statement

None.

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