

*Article*

# Effects on human health of formaldehyde: from reactive airway diseases (bronchial asthma and allergy) to cancer. A protocol for an umbrella review of systematic reviews and meta-analyses

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**Abstract:** Formaldehyde is an organic compound and the simplest form of aldehyde, and is one of the most common indoor pollutants. Since early '80, the National Institute for Occupational Safety and Health (NIOSH) recommends that formaldehyde should be considered a potential occupational carcinogen and that appropriate measures should be undertaken to reduce workers' exposure. The aim of this research is to systematically review the literature about the association between formaldehyde exposure and reactive airway diseases (like asthma and allergy) and the association between formaldehyde exposure and cancer.

Identification of relevant studies to this review will be achieved by electronic databases search of the published literature including: PubMed, Scopus, Web of Science electronic databases. The following keywords will be used: (Formaldehyde) AND (Cancer OR tumor OR neoplasm OR malign); (Formaldehyde) AND (asthma OR allergy OR reactive airway disease).

This umbrella review will furnish a wide overview about the evidences of potential inflammatory and carcinogenetic effects due to formaldehyde exposure.

**Keywords:** human health, formaldehyde, reactive airway disease, bronchial asthma, allergy, cancer, umbrella review.

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## Introduction

Formaldehyde is an organic compound and the simplest form of aldehyde. At room temperature, formaldehyde is a colorless gas with a pungent odor. It can be a main precursor to many other chemical compounds, especially polymers. Formaldehyde is used in the production of formaldehyde resins, particleboard, paper, plywood, and urea-formaldehyde foam (Abdollahi et al, 2014).

A formaldehyde-glutaraldehyde fixative produces useful fixation of a wide variety of cells and tissues. It has been surmised that the formaldehyde would penetrate faster than the glutaraldehyde and temporarily stabilize structures that are subsequently more permanently stabilized by the slower-penetrating, but more efficiently cross-linking, glutaraldehyde (Karnovsky et al, 1965).

Formaldehyde is one of the most common indoor pollutants. The main indoor sources of formaldehyde are wood-pressed products, insulation materials, paints, varnishes, household cleaning products and cigarettes, among others (Rovira et al, 2016).

According to International Agency for Research on Cancer (IARC) Formaldehyde is used like an intermediate product in the chemical industry. It is also present as antimicrobial agent in many cosmetic products (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 88, 2006).

Since early '80, the National Institute for Occupational Safety and Health (NIOSH) recommends that formaldehyde should be considered a potential occupational carcinogen and that appropriate measures should be undertaken to reduce workers' exposure (Blackwell et al, 1981).

The toxicology and epidemiology of formaldehyde were discussed at the 2nd International Formaldehyde Science Conference in Madrid, 19-20 April 2012. It was noted that a substantial amount of new scientific data has appeared since the 1st conference in 2007 (Bolt et al, 2013).

According to the SCOEL (Scientific Committee on Occupational Exposure Limits), formaldehyde can be considered as a "genotoxic carcinogen, for which a practical threshold is supported" and a health-based Occupational Exposure Limit of 0.2 ppm has been recommended (Scientific Committee on Occupational Exposure Limits, 2008).

However, in compliance with recent epidemiological findings, WHO declaims that guideline value of 0,08 ppm formaldehyde is preventive for carcinogenic effects. (World Health Organization, 2000).

In another study, in a cohort of formaldehyde-industry workers, evidence was found of an exposure-response relation with mortality from nasopharyngeal cancer (Hauptmann et al, 2004).

Another study shows that evaluation of risks over time suggests a possible link between formaldehyde exposure and lympho-hematopoietic malignancies, particularly myeloid leukemia but also Hodgkin lymphoma and multiple myeloma (Beane Freeman et al, 2009).

Starting from rat studies, another research describes that the guideline value of the WHO (Air quality guidelines for Europe, 2nd edn. World Health Organization, Regional Office for Europe, Copenhagen, pp 87-91, 2000), 0.08 ppm (0.1 mg m<sup>-3</sup>) formaldehyde, is considered preventive of carcinogenic effects in compliance with epidemiological findings (Nielsen et al, 2010).

Furthermore, a retrospective cohort study evaluated the association between exposure to FA and cancer in professionally potentially exposed in a University setting. The cohort was composed of 140 exposed to FA and 364 not exposed in the period 1999-2015. The results showed no cancers of naso-pharynx and leukemias or lymphomas in both exposed and not exposed samples. These data could be explained by the fact that formaldehyde levels in university laboratories are lower than those used in textile industries (Sernia et al, 2016).

Moreover, *in vitro* studies suggest that formaldehyde may play a role as an irritant of the nasal mucosa by increasing the expressions of adhesion molecules on HMMEC (human mucosal microvascular endothelial cells) and improving the adhesiveness between HMMEC and eosinophils (Kim et al, 2002).

The aim of this research is to systematically review the literature about :

- Association between formaldehyde exposure and reactive airway diseases (like asthma and allergy);
- Association between formaldehyde exposure and cancer.

## **Materials and Methods**

A systematic search will be carried out to assess the association between formaldehyde exposure and reactive airway diseases and cancer, reporting results of the last ten years. Methods for this study were developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al, 2009).

### *Search strategy*

Identification of relevant studies to this review will be achieved by electronic databases search of the published literature including: PubMed, Scopus, Web of Science electronic databases. The following keywords will be used:

- (Formaldehyde) AND (Cancer OR tumor OR neoplasm OR malign)
- (Formaldehyde) AND (asthma OR allergy OR reactive airway disease)

The search will be undertaken with no language of publication restrictions.

### *Study selection*

The review process will consist of a multi-step approach including: title and abstract screening and full-text assessment. Any articles that deemed relevant by the reviewers will be included in the full-text assessment.

Duplicate articles will be filtered using the JabRef 5.2 software. After title and abstract screening, full-text articles will be assessed to determine if they meet the inclusion criteria.

In case an included publication is not available as full-text in English the corresponding author will be contacted to check if the eligible criteria are fulfilled. If no reply is received within 4 weeks the article will be excluded from the analysis.

#### *Inclusion criteria*

The inclusion criteria are described in **table 1**.

**Table 1 – Inclusion criteria of the umbrella review**

<b>Population</b>	<b>Human population exposed to formaldehyde</b>
<b>Phenomena of interest</b>	1) Association between formaldehyde exposure and reactive airway diseases 2) Association between formaldehyde exposure and cancer
<b>Comparators</b>	Any
<b>Outcomes</b>	All
<b>Timing</b>	Last 10 years
<b>Study types and designs</b>	Systematic review and meta-analysis

#### *Data extraction and quality assessment*

Data extraction will be conducted in duplicate by two reviewers independently, extracting data from all included studies.

A data collection sheet will be developed to confirm study relevance and to extract study characteristics.

Study characteristics to be extracted will include: publication year, study design, country, patient population characteristics, formaldehyde exposure effects like cancer and respiratory diseases.

To ensure accurate data collection, each reviewer's independently abstracted data will be compared. Any discrepancies and disagreement will be discussed and resolved through a consensus session with a third researcher.

A quality assessment will be performed using AMSTAR2 for systematic reviews and meta-analyses (Beverley J. et al, 2017).

#### **Conclusions**

The discordant evidences over the time, did not bring to any univocal thesis about the consequences on human health related to formaldehyde's exposure. Potential irritant and carcinogenetic effects are sometimes reported, whilst other studies show that low dose exposure could be recognized as preventive of carcinogenetic effects (Kim et al, 2002, Nielsen et al, 2010, Beane Freeman et al, 2009).

This umbrella review will furnish a wide overview about the evidences of potential inflammatory and carcinogenetic effects due to formaldehyde exposure.

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