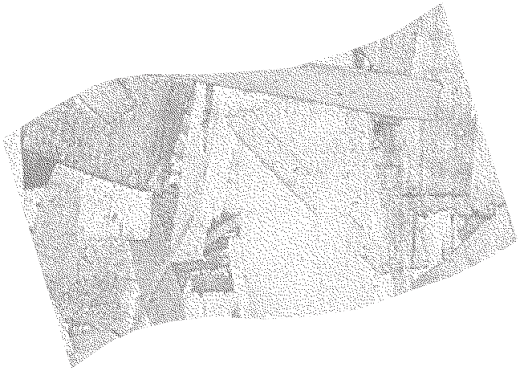
STUDIES AND RESEARCH PROJECTS

APPENDIX

Impact of lowering the permissible exposure value for formaldehyde

Health impact of an occupational exposure to formaldehyde



Gaétan Carrier
Michèle Bouchard
Nolwenn Noisel
Yvette Bonvalot
Sandra Fradet

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IRSST – Communications Division
505, De Maisonneuve Blvd West
Montréal (Québec)
H3A 3C2
Telephone: (514) 288-1551
Fax: (514) 288-7636
www.irsst.qc.ca
Institut de recherche Robert Sauvé en santé et en sécurité du travail,
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Gaétan Carrier, Michèle Bouchard, Nolwenn Noisel
Yvette Bonvalot and Sandra Fradet

Environmental and Occupational Health, Université de Montréal

Clic Research
www.irsst.qc.ca

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 SUMMARY

This annex constitutes the study of the impact on health of lowering the permissible exposure value (VEA) for formaldehyde in the workplace. It is based on the reevaluation of the dose-response relationship between exposure to formaldehyde and the appearance of health effects, based on the set of studies available in literature. A series of criteria was established in order to select and classify the articles according to their scientific qualities, and then statistical analyses were conducted in order to establish this exposure-response relationship for the earliest effects after an acute exposure, i.e. the irritating effects. The health risk or the probability of observing toxic effects attributable to a formaldehyde exposure in workers of Quebec was therefore established by comparing the exposure data collected by the IRSST in the framework of the present study to the exposure-response relationships obtained hereafter. The determination of the risk of cancer after a long-term exposure was obtained by considering dose-response relationships provided by different agencies and by applying them to the Quebec data.

The results showed that workers exposed to formaldehyde concentrations lower than 0.75 ppm should not experience moderate or severe irritating effects to the eyes, nose or throat that may be attributed to formaldehyde. Among the workers exposed to a formaldehyde concentration between 0.75 and <1.0 ppm, 6.3% are likely to experience moderate eye irritations; none would be likely to experience severe eye irritations and 1.6% would have moderate nose and throat irritations. The corresponding values for workers exposed to a concentration of formaldehyde between 1 and < 2.0 ppm are 10.1%, 0.8% and ≈4.5%, as well as 14.9%, 1.9% and ≈12.5% for workers exposed between 2 and 3 ppm (≥ 2 ppm).

On the basis of the epidemiological data in literature and the position of several agencies of toxicological risk evaluation, there is limited evidence of formaldehyde's carcinogenic effects on humans. However, two agencies, the U.S. EPA and the CIIT, tried to quantify the excess risk of cancer on the basis of toxicological data available by using theoretical models of extrapolations of observations from high doses to lower doses. On the basis of animal data, the U.S. EPA suggests an excess unit risk coefficient in the general population for the inhalation of formaldehyde *(inhalation unit risk)* of 1.60×10^{-2} ppm^{-1}. If this coefficient reflected the reality, it would mean that the lifetime excess risk would be 5.3×10^{-6}, for a time-weighted average exposure over 8 hours at 0.016 ppm. On the basis of animal data corroborated by epidemiological data for which excess risk was observed, in 1999 the CIIT suggested an excess risk of cancer in workers at 7.6×10^{-8} for an exposure to 0.1 ppm over 40 years and 0.004 ppm for the remainder of life. The corresponding excess risk for an exposure to 1 ppm over 40 years, 8 hours per day would be 2.1×10^{-4}. The excess risk value for an exposure to 2 ppm was not recorded. The CIIT model was used in estimating the workers' risk of cancer, since it gave the best-fit to the epidemiological data where a positive statistical association was observed.

2 RESEARCH CONTEXT AND OBJECTIVE

The parity-based committee (3.33.1) of the Commission of Health and Occupational Safety (CSST), charged with the revision of Annex 1 of the *Rules on Health and Occupational Safety*, proceeds to the modifications of the RULES by the establishment of a consensus for each of the subjects discussed. In certain cases, members of the committee wish to have better knowledge regarding the impact of their decisions on the health and safety of workers, the technical ease or difficulty of enacting these regulating modifications, and the socio-economic context of Quebec industries and agencies subject to these modifications. Lowering the permissible exposure value for formaldehyde is one of these cases. The CSST therefore asked the IRSST to assess the socio-economic and health impact of such a lowering.

Overall, the project aims to evaluate the impact of lowering the current permissible exposure value (VEA) for formaldehyde, whose ceiling is fixed at 2 ppm, to a VEA ceiling value or weighted average of 1, 0.75 or 0.3 ppm. This objective includes a study of the socio-economic as well as health impact.

The present annex therefore constitutes the study of the impact on health of decreasing the permissible exposure value for formaldehyde in the workplace. In theory, to determine this impact on health of decreasing the current VEA of 2 ppm ceiling, we must first be capable of estimating with acceptable precision the “dose-response” relationship for toxic effects at concentrations of 2, 1, 0.75 or 0.3 ppm either as ceiling value or weighted mean exposure value. This means one must determine the probability of appearance of irritation at these concentrations but also of toxic deleterious effects that are either carcinogenic or non-carcinogenic. The objective of this study was therefore to estimate as precisely as possible, and based on literature data, the dose-response relationship between exposure to formaldehyde and the appearance of health-related effects in workers within the concentration ranges considered as permissible values, in order to determine the benefit that a lowering in permissible values might bring to the workers’ health. In this respect, the different toxic effects of formaldehyde observed or suspected at levels close to the current standard and the degree of severity of these effects were examined, and the emphasis was placed on the earliest effects to occur in the most sensitive individuals.

3 INTRODUCTION

3.1 Source and exposure to formaldehyde

Formaldehyde is a substance frequently used in industrial settings such that numerous workers are regularly exposed to it. As a consequence, numerous workers, in industries of different types, are exposed to concentrations particularly high in formaldehyde. However, formaldehyde is well known for causing harmful effects on the health of the individuals exposed, and notably irritations to the skin, mucus membranes, eyes, nose, and respiratory tract. It is also suspected to be a causal agent of certain types of cancer. This is why it is important to know precisely the health-related effects produced by formaldehyde, as well as the airborne concentration at which these harmful effects are susceptible to appear.

In the workplace, exposure to formaldehyde occurs mainly via the respiratory tract. Formaldehyde can also be absorbed to a limited extent after contact with skin. The cutaneous effects appear as red spots, itches, irritations, allergic reactions, or dermatitis (1, 2). Since the impact study concerns the establishment of a limit value for an airborne exposure, only the effects of exposure to formaldehyde by the respiratory tract were considered. Furthermore, individual protection, such as wearing adapted gloves, allows the wearer to easily avoid the cutaneous effects.

Formaldehyde can cause effects that alter the health of persons exposed. It is possible to distinguish the appearance of different effects according to the duration and intensity of exposure. The nature of the effects will therefore be different depending whether the exposure was a single short-term exposure, also called acute exposure, or whether it was a repeated long-term exposure of a chronic nature. This section will concurrently examine effects due to acute, subchronic and chronic exposures. Furthermore, there is a whole gradation of the severity of the effects, from the mildest to the most severe, which is the result of different degrees of exposure to formaldehyde. There are also important variations between individuals with respect to the appearance of symptoms experienced (3).

The exposure cannot be easily evaluated by measures of internal concentrations of formaldehyde such as blood concentration because bioavailable formaldehyde at the site of contact is directly converted into formate (4); therefore, in the case of a respiratory tract exposure, the blood concentration of formaldehyde would be practically nonexistent. Formaldehyde is also the metabolite of many other chemical products used in the workplace, such as methanol (5). Indeed, methanol absorbed by inhalation is quickly biotransformed in the body into formaldehyde, which quickly undergoes a biotransformation into formate then into carbon dioxide. Furthermore, formaldehyde in the body may come from the biotransformation of certain foods or drinks; the internal measures would therefore not allow for differentiation between endogenous formaldehyde (metabolite of other substances) and exogenous formaldehyde. Hence, the only possible way is to measure the concentrations in the air in order to estimate exposure to formaldehyde in the workplace.

3.2 Health effects of formaldehyde

3.2.1 Effects due to acute exposure

Generally, the effects due to an acute exposure induced by formaldehyde affect the conjunctiva and respiratory airways, particularly the upper airways, due to its physicochemical properties (greater solubility in water) and to the proximity of this contact zone. The first effects are eye, nose and throat irritations (6-14). Based on this fact, the dose-response relationship established in the present study is determined solely from these irritating effects. Several authors reported that the irritating effects of formaldehyde are reversible: the irritating effect subsides and disappears after the exposure has stopped (3, 14). Furthermore, a tolerance to irritations may appear with time (15). However, for all of the irritating effects mentioned above, there is a great variability of responses and individual sensitivities may differ significantly (3). Hence, this makes it necessary to reevaluate all of the available data concerning the relationship between the degree of exposure to formaldehyde and the appearance of irritating effects.

3.2.2 Effects due to a subacute to subchronic exposure

The main effects suspected to be related to subchronic exposure to formaldehyde are alteration of pulmonary function, induction of asthma attacks and appearance of chronic bronchitis in exposed subjects (8, 9, 13, 16-19). Like in the case of acute effects, for subchronic effects, there are also significant variations in individual susceptibility.

3.2.3 Effects due to chronic exposure

Many epidemiological studies have been conducted to verify if there is a link between exposure to formaldehyde and the appearance of certain types of cancer. Most of the epidemiological studies aiming to verify the link between exposure to formaldehyde and the increase in the incidence of cancer have dealt with sites directly in contact with inhaled formaldehyde: the sinus and nasal passages (20-27), the oral cavity and pharynx (28, 29), the oropharynx (24), the nasopharynx (24, 26, 27, 29-35), the larynx (36, 37) and the conjunctive tissues of the nasal passages (38).

Certain studies have also dealt with sites of cancer with no direct contact with inhaled formaldehyde: cancer of the bile and hepatic ducts as well as cancer of lymphatic and hematopoietic sites (39). In certain isolated and sporadic cases, diseases such as multiple myeloma, non-Hodgkin's lymphoma, ocular melanoma, leukemia, brain, colon and pancreatic cancer were associated with formaldehyde (38, 40-42). However, these cases have to be considered with much caution since the biological plausibility of these connections is extremely low.

3.2.4 Position of reference and regulatory organizations

The National Institute of Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), the American Conference of Governmental Industrial Hygienists (ACGIH) and the U.S. Environmental Protection Agency (U.S. EPA) have all proposed exposure limit values for formaldehyde based on toxicological animal studies as well as available epidemiological studies. The International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) have given special attention to the question of formaldehyde's carcinogenic potential. Moreover, it is interesting to note that, from these organizations, only OSHA is an organization with regulatory power.

3.2.4.1 National Institute of Occupational Safety and Health (NIOSH)

Historically, the first criteria were proposed by NIOSH in 1976. At that time, formaldehyde was not considered carcinogenic by this organization, and the recommended level was a formaldehyde concentration of 1 ppm in ambient air for any sample period of 30 minutes (43).

As of 1981, NIOSH recommended that formaldehyde should be handled like any other potential professional carcinogen and that appropriate control measures should be implemented so as to reduce the exposure of workers. Their recommendations were mainly based on the results of a study from the Chemical Industry Institute of Toxicology (CIIT) in which rats and mice exposed to inhaled formaldehyde had developed nose cancers (44) following chronic exposure to air concentrations higher than 5 ppm. It was only in 1988 that NIOSH recommended an 8-h time-weighted average exposure limit (REL or recommended exposure limit) of 0.016 ppm taking into account the carcinogenic potential of formaldehyde, and of 0.1 ppm as a ceiling value determined on any sample of 15 minutes (45). These limits were determined by using a theoretical high-to low dose extrapolation model, by issuing the hypothesis that the risk is never null, even for low doses, which is an unverifiable hypothesis.

3.2.4.2 Occupational Safety and Health Administration (OSHA)

As for OSHA, it established a permissible exposure limit (PEL) in all workplaces (industry in general, construction, naval industry, agriculture excluded) of 0.75 ppm as an 8-h time-weighted average exposure, and of 2 ppm as short-term exposure limit (maximum allowed exposure over 15 minutes). The OSH *Act* also defines a set action level at 0.5 ppm and expressed as a weighted exposure average over 8 hours. This action level requires, among other things, implementation of supervision and follow-up procedures when exposure exceeds this value (46). OSHA also labeled formaldehyde as a potential human carcinogen causing nose and lung cancer, as well as having other possible links to other types of cancer (brain and leukemia) (47).

3.2.4.3 American Conference of Governmental Industrial Hygienists (ACGIH)

From 1983 to 1991, the proposed TLV or threshold limit values were an 8-h time-weighted average weighted exposure of 1 ppm and a short-term exposure limit value of 2 ppm. But as of 1989, ACGIH proposed the cancellation of these two TLVs (TLV-TWA and TLVSTEL) in order to replace them with a ceiling type threshold limit value (TLV-ceiling) of 0.3 ppm based on the irritating effects reported in the professional environment as well as in other environments. By this proposal adopted in 1992, ACGIH did not expect to see the complete disappearance of complaints due to irritations associated with an exposure to this component, but that these would significantly diminish in number.

Furthermore, ACGIH proposed to classify formaldehyde as an A2 carcinogen as of 1981, a proposal that was adopted in 1985 (48). This qualitative classification of the carcinogenic potential of formaldehyde signifies that ACGIH considers it a potential human carcinogen. In fact, for ACGIH this definition is mainly used when the proof of the carcinogenic potential is limited on the basis of human data but sufficient on the basis of experimental data (49). Still in effect in 1998 (50), in 1999 ACGIH proposed a modification to its recommendations that remain similar for the moment to those of 1992-1998. In addition to still considering formaldehyde as a potential carcinogenic for humans (classification A2), ACGIH proposes to indicate that this component presents, on the basis of available scientific knowledge, a confirmed potential sensitivity either by dermal contact or by inhalation (49).

3.2.4.4 U.S. Environmental Protection Agency (U.S. EPA)

The last review carried out by the U.S. EPA on formaldehyde dates back to 1991 (51). A reference dose was then proposed for the ingestion of formaldehyde but none seems to be available for inhalation. On that occasion, the carcinogenic potential of formaldehyde was also reviewed and formaldehyde was classified in group B1, as a substance likely to be carcinogenic for man according to limited human testing and insufficient animal testing (51). For this organization, at least nine studies have demonstrated a significant association between specific sites of respiratory neoplasms and exposure to formaldehyde or to products containing formaldehyde. As for the long-term animal studies, they demonstrated an increase in the incidence of nose squamous cell carcinoma. Furthermore, the *in vitro* data on the genotoxicity of formaldehyde as well as its structural proximity to other carcinogenic aldehydes, such as acetaldehyde, support this classification.

From a quantitative point of view, in 1991 the U.S. EPA proposed an excess unit risk coefficient for inhalation of formaldehyde (inhalation unit risk) of 1.3×10^{-5} $(\mu g/m^3)^{-1}$ or even of 1.60×10^{-2} ppm^{-1} (knowing that 1 mg/m^3 is equal to 0.81 ppm). This excess unit risk coefficient serves to estimate the cancer risk for low doses. The U.S. EPA revised its position the same year, in 1991, and integrated various aspects that were not presented in the fact sheets supplied by IRIS (52). Following this work, in 1991, the U.S. EPA proposed an excess unit risk coefficient for inhalation of formaldehyde of 2.7×10^{-7} $(\mu g/m^3)^{-1}$ or even 3.3×10^{-4} ppm^{-1} (53).

3.2.4.5 International Agency for Research on Cancer (IARC)

The last monograph produced by the IARC to evaluate the carcinogenic effects of formaldehyde dates back to 1995 (54). However, a reevaluation taking into account very recent studies made CIRC classify formaldehyde as carcinogenic to humans (group 1) on the basis of sufficient indications of carcinogenicity (rhinopharynx) arising from epidemiological studies.

3.2.4.6 National Toxicology Program (NTP)

The NTP also has a qualitative classification of the carcinogenic potential of substances that they study. This classification is made up of two categories: that of substances known to be human carcinogens, and that of substances reasonably expected to be human carcinogens. Formaldehyde is classified in the second category of the NTP (55). According to the NTP, there is sufficient proof for the carcinogenic potential of gaseous formaldehyde in animals. Moreover, the NTP indicates that when this component is administered by inhalation, it leads to squamous cell carcinoma of the nasal cavity in rats of both sexes. With respect to human data, the NTP concludes, like the IARC, that they are limited, even though several studies observed a statistical association between exposure to formaldehyde and a prevalence of cancer, particularly of the nose and nasopharynx. Certain methodological limits lead to this cautious conclusion.

4 METHODOLOGY

The effects on health caused by formaldehyde vary according to the nature of the exposure, acute, subchronic or chronic. Therefore, a distinctive methodology was adopted to study the effects associated with these different types of exposure.

4.1 Methodological approach for the effects due to acute exposure

In general, the global approach adhered to is the following:

- determination of a dose-response or exposure-response relationship based on data available in literature;
- application of the dose-response relationship to the data on exposure to formaldehyde in the various industrial sectors of Quebec;
- determination of the health impact of lowering the standard to 1.0, 0.75 or 0.3 ppm.

4.1.1 Determination of a dose-response or exposure-response relationship based on data available in literature

The relationship between acute exposure to formaldehyde and the appearance of toxic effects on health was established based on data available in literature. The articles concerning formaldehyde are numerous and of variable quality which demands the establishment of rigorous selection criteria so as to select the articles that allow the establishment of this dose-response relationship. The available studies are of two types: controlled studies and studies carried out in the workplace.

4.1.1.1 Selection of articles and collection of data on exposure to formaldehyde and associated effects

The selected articles met the following criteria:

- exposure only to formaldehyde;
- exposure concentrations varying from at least 0 to 2 ppm since the problematic of this report concerns this segment of values.

The selected articles were then classified according to their scientific quality by attributing three levels of confidence: 1) low or moderate, 2) moderately high, 3) high.

Controlled studies were automatically attributed a relatively high degree of confidence (moderately high to high) because the formaldehyde concentrations are measured throughout the study so as to determine, with precision, the true exposure of the subjects. A high degree of confidence was attributed to any controlled double-blind study, with a control group and whose effects were evaluated based on objective criteria. A moderate degree of confidence was attributed to any controlled study having at least one of the following criteria: double-blind study, study with a control group, study evaluating the effects based on objective criteria. The realization of a double-blind study implies that neither the subjects nor the personnel conducting the study know who is exposed and to what concentration, so as to not bias the results. The presence of a control group allows knowledge of the rate of appearance of the effects for a non-exposed population as well as the real effects of formaldehyde. The evaluation criteria of the effects considered as objective are measurable values such as blinking frequency observed by an outside party unknown to the subjects, the measure of forced pulmonary capacity and forced expiratory volume, the observation of histological changes in nasal secretions. Subjective criteria consist of the questionnaires and responses related to subject

perception (perception of odor, of irritation, the need to leave the premises, to open the windows, etc.).

Studies carried out in the workplace were attributed a low degree of confidence (generally moderate) because the exposure was not controlled and the level of exposure could vary.

For the two types of studies, those where the protocols were less rigorous and were attributed a low degree of confidence were automatically rejected.

The following data were then summarized for each of the selected studies:

- the study population (number of subjects, sensitivity or non-sensitivity of subjects…);
- the exposure conditions (degree and duration of exposure, presence or not of exercise, continuous or intermittent exposure);
- the measured effect, its severity and the percentage of response of the subjects to this effect, the evolution based on the time;
- the methodology followed (means of evaluation of the exposure and its effects, presence of a control group, double-blind study);
- the control or the presence of confounding factors (room temperature, level of humidity, rate of air exchange, presence of other substances, smoking).

4.1.1.2 Usage of literature data to establish the dose-response relationship

The relationship between acute formaldehyde exposure and the appearance of effects was established based on the collection of all rough data from each of the studies considered to have a degree of confidence moderately high to high. Hence, these studies are all led in a controlled setting. Moreover, the effects selected for the establishment of a dose-response relationship are the irritating effects to the eyes and airway mucosa (nose and throat) as well as perception of odor. These effects are most frequently reported following an acute exposure to formaldehyde suggesting that they are the critical effects (those that appear with the lowest concentrations).

For each of the controlled studies, the number of subjects presenting irritating effects, according to the class of exposure and the severity of the effect, was listed. The degree of exposure was fractioned into six distinct classes: from 0 to <0.3 ppm, from 0.3 to <0.75 ppm, from 0.75 to <1.0 ppm, from 1.0 to <2.0 ppm, from 2.0 to <3.0 ppm, and >3.0 ppm (which in fact combined the exposures between 3.0 and 4.0 ppm). The effects studied are, as indicated previously, eye, nose and throat irritations as well as the perception of odor. Since the classification of the severity of the effects is not the same from one study to another, it was necessary to define three categories of effects in order to combine the totality of the studies. These three classes are as follows: 1) little or no effect, 2) moderate effect, tolerable to annoying, 3) severe effect.

With respect to uncontrolled studies, that is to say studies carried out in the workplace, a systematic analysis of the literature was also performed. For these studies, in general, there was no data on the severity of the effects (only presence or absence of effect). Moreover, the degree of exposure was not reported with precision. More often, the exposure was characterized by the range and the average or median, and sometimes a few peak values were offered. Since these studies demonstrated a lesser degree of confidence, they were not integrated in the establishment of the dose-response relationship. They served solely to support the results of the controlled studies.

4.1.1.3 Establishment of the dose-response relationship

By combining the data from the different controlled studies, a global dose-response relationship was established. More specifically, the total number and the proportion of subjects presenting irritating effects by type of effects, severity of effects and class of exposure were compiled in the form of a table by adding the numbers of the different studies. This data allowed the creation of dose-response curves where the background noise value, that is to say the frequency of irritations in the absence of exposure, was subtracted. This graphic chart allowed to carry out correlation/regression analyses so as to determine the mathematical model allowing the best-fit to the experimental data. The tested models are degree 2 to 4 linear and polynomial regressions.

4.1.2 Application of the dose-response relationship to the data on exposure to formaldehyde in different industrial sectors of Quebec

The expected theoretical response percentages (irritating effects according to the degree of exposure) in workers from various industrial areas of Quebec were estimated with the help of models obtained in the previous stage. This stage allowed the outline of the global impact of exposure to formaldehyde on the health of Quebec-based workers in terms of frequency and severity of effects.

4.1.3 Determination of the impact on health of lowering the standard to 1.0, 0.75 or 0.3 ppm

The impact on health was determined by estimating, for each class of exposure, the theoretical number of workers for whom the irritating effects could potentially be avoided after a decrease in the degree of exposure.

4.2 Methodological approach for the effects due to subacute to subchronic exposure

The studies available to evaluate of the effects of formaldehyde on the pulmonary function, on onset of asthma attacks and on sensitivity were essentially the same as those that allowed the evaluation of the effects of formaldehyde following an acute exposure. These studies were registered and analyzed so as to outline the global tendency of these studies.

4.3 Methodological approach for the effects due to chronic exposure

4.3.1 Literature review

A list of different epidemiological studies (case-control, cohort or meta-analysis types), dealing with the relationship between formaldehyde and upper airway cancer in humans, was established. The types of cancer evaluated in the studies are cancer of the nasal passages, pharynx, larynx and oral cavity, given the strong biological plausibility of these types of cancer demonstrated in the experimental animal studies. The list of selected studies was modified when other pertinent studies were obtained or when studies were deemed non-pertinent after review, according to the following exclusion criteria.

4.3.2 Exclusion criteria

Studies dealing with cancer sites other than cancer of the nasal passages, pharynx, larynx and oral cavity, as well as studies dealing with populations included in more recent studies have not been evaluated. Furthermore, studies that did not evaluate the exposure to formaldehyde separately as compared to other professional exposures were not considered. In fact, the studies that did not allow for the incrimination of formaldehyde as a causal agent were rejected. In the case where professional exposure to substances other than formaldehyde would have been controlled, the study would be selected; however, this case did not occur.

Following these criteria, a total of 33 epidemiological studies were selected (types of studies: 18 case-control, 12 cohort and 3 meta-analysis studies).

4.3.3 Analysis Measures

The selected epidemiological studies were read, summarized, analyzed and critiqued. A first analysis was carried out according to specific criteria (quality of classification of those exposed and of their degree of exposure, real environmental measures versus questionnaires, quality of the classification of illnesses, cases and controls, power of the study, control of confounding factors, presence of a dose-response relationship, etc.) with the aim to classify the studies according to their quality and, hence, to eliminate those whose quality is such that no valid conclusion could be extracted. Those selected were further analyzed to verify whether the obtained results permitted the conclusion, with a certain degree of confidence, that formaldehyde has carcinogenic potential in humans, and if so, from what levels of exposure.

A critique of various articles and a classification according to their scientific quality seem to constitute an essential step. Conclusions are based on studies where precision and validity are high.

Following this analysis, the studies were grouped by type (cohort, case-control or meta-analysis). The results of each study taken individually were analyzed by scrutinizing their strengths and their weaknesses in an attempt to verify the accuracy of their conclusion. Hence, the points verified systematically were the power of the study, its precision, and the quality of the evaluation and the classification of the exposure of the studied groups, the quality of the classification of effects, the concordance of the observed effects between the studies, and the control, or not, of the confounding or potentially modifiable factors. Methodological limitations associated with these aspects often lead to a detailed explanation of risk results observed in epidemiological studies.

In order to evaluate the causal relationship between exposure to formaldehyde and the risk of upper airway cancer, all studies were analyzed by verifying if the Hill criteria apply: strength of the association between cancer and exposure, consistency between results of various studies, temporality, biological plausibility, existence of a gradient in the dose-response (or dose-effect) relationship and specificity of effects.

5 RESULTS

5.1 Irritating effects due to acute exposure to formaldehyde

5.1.1 Synthesis of literature data

Table 1 summarizes all registered and studied characteristics for the studies where the degree of confidence seemed acceptable and which were selected.

Table 2 describes, for each of the selected controlled studies, the number of subjects who experienced irritating effects (mild, moderate or severe) of the eyes, nose and throat and who perceived odor according to the degree of exposure. The data in these tables indicate that the response percentages and the degree of severity of analyzed effects vary very little according to the duration of exposure (90 seconds to 3 hours).

Table 3 reports the number and percentage of workers presenting irritating effects, for each study carried out in the workplace and selected. These tables show similar results between the controlled studies and those carried out in the workplace.

All studies used are described in detail in Appendix 1.

Table 1: Summary of the principal characteristics of controlled studies and of studies carried out in the workplace showing a reasonable degree of confidence

Study	Study Population	Exposure	Response				
			Measured effect	Severity of the effect	% of irritating effect response	% of response for controls	Time evolution
Green *et al.*, 1987, in inhalation chamber	38 non-smoking subjects, of which 22 healthy and 16 asthmatics	Continuous exposure to 0 and 3 ppm, with and without exercise	Eye irritation	moderate to severe	27% healthy subjects and 19% asthmatics		
			Nose and throat irritation	moderate to severe	32% healthy subjects and 31% asthmatics		
			Odor	moderate to severe	23% healthy subjects and 31% asthmatics		
Harving *et al.*, 1990, in inhalation chamber	15 non-smoking, asthmatic subjects	Exposure to 0.06; 0.1 and 0.7 ppm (0.008; 0 .12 and 0.85 mg/m^3), for 90 min.	Pulmonary function and asthma				
Kulle *et al.*, 1987, in inhalation chamber	15 non-smoking, healthy subjects	Exposure to 0; 0.5; 1; 2 and 3 ppm continuously for 3 hrs., with an exercise period at 2 ppm	Eye irritation	mild to moderate	At 0.5ppm= 0%, at 1 ppm= 26%, at 2 ppm=53%, at 3 ppm= 100%	0 ppm=5%	
			Nose and throat irritation	mild to moderate	At 0.5 ppm= 10%, 1 ppm= 5%, 2ppm= 37%, 3 ppm= 22%	0 ppm=16%	
			Perception of odor	mild to severe	At .5 ppm= 40%, 1 ppm=26%, 2ppm=58%, 3 ppm=78%	0 ppm=5%	
Kulle, 1993, in inhalation chamber					Reanalysis of 1987 study		
Nordman *et al.*, 1985, in inhalation chamber	12 asthmatic subjects (the number of smokers is not documented)	Exposure to 1 and 2 ppm (1.2 to 2.5 mg/m^3) for 30 min.	Bronchial challenge test				
Pazdrak *et al.*, 1993, in inhalation chamber	9 sensitive subjects (known to have, among other things, skin sensitivity), exposed to formaldehyde in the workplace, non-smokers	Exposure to 0.4 ppm (0.5 mg/m^3), for 2 hrs.	Changes in nasal secretions				
Pross *et al.*, 1987, in inhalation chamber	23 asthmatic subjects (the number of smokers is not documented) living in UFFI insulated homes	Exposure to 1 ppm of formaldehyde for 3 hrs, then at 1 ppm UFFI particles, without physical exercise	Immunological and hematological changes				
Reed and Frigas, 1985, in inhalation chamber	13 sensitive subjects (asthma or sensitivity to formaldehyde) of which 5 are smokers	Exposure to 0.1, 1 and 3 ppm for 20 min.	Bronchial challenge test				
Sauder *et al.*, 1986, in inhalation chamber	9 healthy, smoking subjects	Continuous exposure to 0 and 3 ppm, for 3 hrs., with 8 min. of physical exercise (bicycle)	Eye irritation	from none to moderate	11% (1/9) moderate irritation of the eyes, 1/9 no symptom, 7/9 mild irritation, i.e. 78%. Total irritation 11%+78% = 89%	0% at 0 ppm	Stronger effect after 30 min. than after 60 min.
			Nose and throat irritation	from none to moderate	56% moderate nasal and throat irritation and 33% mild irritation. Total throat irritation (mild + moderate) 89%		
			Perception of odor	from none to moderate	44% odor perception		

ND: Not Determined

Study	Methodology				Confounding factors					Remarks
	Exposure evaluation	Evaluation of effects	Control group	Double blind	Room temperature	Level of humidity	Rate of air exchange	Wood dust	Other substances	
Green *et al.*, 1987, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	ND	22.2±0.5°C	60±2%	7 m^3/min (3.2 min)	No	No	Evaluating the effects of formaldehyde with and without exercise allows us to see the impact from the change in respiration. From the 38 subjects, 5 demonstrated a drop in pulmonary function of more than 10%. The group of asthmatics did not show any significant decrease in pulmonary function.
Harving *et al.*, 1990, in inhalation chamber	Acetyl acetone method		Subjects exposed to 0 ppm serve as control	Double blind	22.9±0.4°C	45,.±0,.%	ND	No	No	The study concludes in an absence of formaldehyde effect on the respiratory function. Irritation was not studied.
et al., 1987, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	ND	22.2±0.5°C	60±2%	7 m^3/min (3.2 min)	No	No	No symptoms reported 24 hrs. after exposure. Threshold of odor perception <0.5 ppm, eye irritation between 0.5 and 1ppm, 1 ppm for nasal and throat irritation.
Kulle, 1993, in inhalation chamber										This article reevaluates the previous one.
Nordman *et al.*, 1985, in inhalation chamber	Chromotropic acid method	Serology, spirometry	No		Uncontrolled	Uncontrolled	No air exchange	No	No	The 12 asthma cases were indexed as being directly linked to the presence of formaldehyde, from a cohort of 230 persons. No data on irritation. (The inhalation chamber allows bronchial challenge test in a controlled environment.)
Pazdrak *et al.*, 1993, in inhalation chamber	Not specified	Analysis of secretion cells	11 healthy subjects not exposed at work	Single blind	ND	ND	ND	No	No	The study concluded to a non specific, non allergenic inflammation due to formaldehyde. Irritation is mentioned (even for concentrations of 0.4 ppm), but not quantified. No significant changes in nasal secretions.
Pross *et al.*, 1987, in inhalation chamber	Chromotropic acid method	Blood tests	4 asthmatic subjects not living in an UFFI insulated house	Lab personnel do not know the origin of the samples	ND	ND	ND	No	Bacteria found in the insulation foam	The study does not deal with irritations. Hematological changes are low. Immunological changes do not allow the conclusion that formaldehyde provokes asthma. Germs found in the insulation foam of certain homes lead us to believe that they are at the source of inhabitants' complaints.
Reed and Frigas, 1985, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	Partially (sometimes single blind)	ND	ND	ND			No data on subjects irritation. Formaldehyde did not induce an asthma attack in any of the 13 asthmatic subjects.
Sauder *et al.*, 1986, in inhalation chamber	Chromotropic acid method	Plethysmography, spirometry, questionnaire (scale of 0 to 3)	Each subject is his/her own control	ND	22.2 ± 05 °C	60±2%	7.0 m3/min (complete change in 3.2 min)	No	No	Slight decrease in FEF and FEV after 30 min. (but not significant after 60 and 180 min.) for exposure at 3 ppm. Effects on throat and nose felt more severe than those on the eyes.

ND: Not Determined

Study	Study Population	Exposure	Response

			Measured effect	Severity of the effect	% of irritating effect response	% of response for controls	Time evolution
Sauder *et al.*, 1987, in inhalation chamber	9 non-smoking, asthmatic subjects	Exposure to 0 and 3 ppm, for 3 hrs., continuously and without physical exercise	Eye irritation	mild or moderate but tolerable	78%	17% on average	after 120 min., gradual effect
			Eye irritation	moderate (annoying)	11%		after 120 min., gradual effect
			Nose and throat irritations	mild or moderate but tolerable	89%	22%	after 60 min., gradual effect
Schachter *et al.*, 1986, in inhalation chamber	15 healthy, non-smoking subjects	Exposure to 0 and 2 ppm for 40 min., an exposure with exercise (10 min.) and a continuous exposure without exercise	Pulmonary function and irritations	mild to moderate, rarely severe, never disabling	Eye irritation, at rest = 53%, activity 7/15 = 47% nasal irritation, at rest = 40%, activity = 33% sore throat, at rest = 27%, Activity = 33% odor, at rest = 80%, activity = 87% taste, at rest = 33%, activity = 40%	At rest = 0%, activity = 7% At rest = 27%, activity = 14% At rest= 14%, activity = 0% At rest = 47%, activity = 14% At rest = 14%, activity = 7%	Symptoms of irritation diminish after 30 min. of inhalation
Schachter *et al.*, 1987, in inhalation chamber	15 healthy subjects, workers exposed on a daily basis to formaldehyde, of which 3 are smokers	Exposure to 0 and 2 ppm for 40 min., an exposure with exercise (10 min.) and a continuous exposure without exercise	Pulmonary function and irritations	mild to moderate, often severe	Eye irritation, at rest = 47%, activity = 40% nasal irritation, at rest = 0%, activity = 7% sore throat, at rest = 0%, activity = 0% odor, at rest = 80%, activity = 87% taste, at rest = 20%, activity = 27%	At rest = 0%, activity = 0% At rest=7%, activity = 0% At rest = 7%, activity = 0% At rest = 47%, activity = 33% At rest = 7%, activity = 7%	
Weber- Tschopp *et al.*, 1977, in inhalation chamber	81 healthy subjects: 33 at continuous exposure and 48 at intermittent exposure	Exposure between 0.03 and 4 ppm, 37 min. duration for a continuous exposure and 1.5 min. duration for an intermittent exposure (exposure to 0.03; 1.2; 2.1; 2.8 and 4.0 ppm)	Blinking frequency and other subjective irritating effects		At 0.5 ppm, for HCHO only, % moderate eye irritation =2%, severe = 0, blinking frequency doubled in 11%. For values of 2.1 ppm, moderate eye irritation in 10%, strong eye irritation in 7%, blinking frequency doubled in 33%.		
Witek *et al.*, 1986, in inhalation chamber					The results are reviewed and further analyzed in detail in the studies of Schachter *et al.*, 1986 and Witek *et al.*, 1987		
Witek *et al.*, 1987, in inhalation chamber	15 non-smoking, asthmatic subjects	Exposure to 0 and 2 ppm for 40 min., an exposure with exercise (10 min.) and a continuous exposure without exercise	Pulmonary function and irritations	mild to moderate, often severe	Eye irritation, at rest = 73%, activity = 33% nasal irritation, at rest = 47%, activity = 33% sore throat, at rest = 33%, activity = 40% odor, at rest = 100%, activity = 93% taste, at rest = 60%, activity = 53%	At rest = 7%, activity = 14% At rest = 20%, activity = 14% At rest = 27%, activity = 20% At rest = 33%, activity = 53% At rest = 14%, activity = 7%	

ND: Not Determined

Study	Methodology				Confounding factors					Remarks
	Exposure evaluation	Evaluation of effects	Control group	Double blind	Room temperature	Level of humidity	Rate of air exchange	Wood dust	Other substances	
Sauder *et al.*, 1987, in inhalation chamber	Colorimetric and chromotropic acid method	Questionnaire (scale from 0 to 5) Spirometric measures, bronchial challenge, plethysmo-graphy	Subjects at 0 ppm	ND	22.2±0.5°C	60±2%	5.7 m^3/min (4 min)	No	No	Study that underlines the increase of effects with time. The maximum effects appear after 60 (nose/throat) or 120 min. (eyes), then remain stable or lightly diminish. Significant increase in nose and throat irritation after 30 min. and of eyes after 60 and 180 min. 3 ppm does not entail any bronchoconstriction in asthmatics at rest. Asthmatics are no more sensitive to formaldehyde than healthy individuals. No significant change in pulmonary function (FVC, FEV1, FEF25-27%, Sgaw, FRC.)
Schachter *et al.*, 1986, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	Double blind	23±0.2°C	50%	ND	No	No	No change in pulmonary function after acute or subacute exposure (at rest or during exercise). The most frequent non-respiratory symptom is eye irritation.
Schachter *et al.*, 1987, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	Double blind	23°C	50%	ND	No	No	No acute pulmonary effects at 2 ppm. Subjects complain more often of irritation or discomfort (odor, taste…). Irritating effects are generally very mild.
Weber-Tschopp *et al.*, 1977, in inhalation chamber	Chromotropic acid method	Measure of the rate of eye-blinking and subjective criteria	Yes	ND			0.1	No	No	Starting from 1.7 ppm, there is a significant difference in the eye blinking frequency (as compared to the controls), but at 3.2 ppm this frequency has not yet doubled. Significant difference: eye irritation (1.2 ppm), nose irritation (1.2 ppm), throat irritation (2.1 ppm), eye-blinking frequency (1.7 ppm). The results of discontinued exposure are not much dif-ferent from those of a continued exposure. For the cigarette smoke containing 0.5 formalde-hyde, moderate eye irritation 36%, severe 27%, eye-blinking frequency doubled 78%.
Witek *et al.*, 1986, in inhalation chamber										The conclusions are the same as in the articles from Schachter *et al.*, 1986 and Witek *et al.*, 1987.
Witek *et al.*, 1987, in inhalation chamber	Chromotropic acid method	Questionnaire and spirometry	Subjects at 0 ppm	Double blind	23°C	50%	ND	No	No	Moderate asthmatics exposed to 2 ppm of formaldehyde do not develop acute or delayed bronchoconstriction. Subjects complained of irritation (eyes, nose and throat) that disappeared after exposure had stopped.

ND: Not Determined

Study	Study Population	Exposure	Response				
			Measured effect	Severity of the effect	% of irritating effect response	% of response in controls	Time evolution
Alexandersson and Hedenstierna, 1988, paint (lacquer) industry workers	38 study subjects, of which 19 are smokers. The number of healthy and sensitive individuals was not stated.	Exposure between 0.11 and 2.1 ppm (0.14 and 2.60 mg/m^3), average to .32 ppm (0.4 mg/m^3) and average peaks to 0.56 ppm (0.7 mg/m^3)	Eyes		25%	3%	
			Nose and throat		15%	0%	
Alexandersson and Hedenstierna, 1989, wood industry workers	34 study subjects, of which 17 are smokers. The number of healthy and sensitive individuals was not stated (some were exposed to t = 0, but not exposed to t = 5 years)	Exposure between 0.34 and 0.4 ppm (average between 0.42 and 0.50 mg/m^3), 6 to 7 hr. per day, at t = 0 and at t = 5 years	At t=0, eyes: smarting		68% (N=34)	0% (N=19)	
			Itching eyes		16% (N=34)	0% (N=19)	
			Running eyes		50% (N=34)	0% (N=19)	
			Running nose		11% (N=34)	0% (N=19)	
			Dryness nose		8% (N=34)	0% (N=19)	
			decrease sense of smell		28% (N=34)	0% (N=19)	
			At t=5 years, eyes:smarting		45% (N=21)	30% (N=32)	
			Itching eyes		40% (N=21)	37% (N=32)	
			Running eyes		60% (N=21)	42% (N=32)	
			Running nose		30% (N=21)	22% (N=32)	
			Dryness nose		15% (N=21)	6% (N=32)	
			decrease sense of smell		0% (N=21)	0% (N=32)	
Boysen *et al.*, 1990, chemical plant workers	37 subjects (the number of smokers are a controlled factor, but not published)	Exposure between 0.5 and >2 ppm (the majority <2 ppm)	nose irritation		14%	0%	
Edling *et al*., 1987, wood industry workers	75 exposed subjects (number of healthy or sensitive subjects and nature of sensitivity unspecified), of which 26 are smokers	Exposure to TWA between 0.08 and 0.88 ppm (0.1 and 1.1 mg/m^3) with peaks at 4 ppm (5 mg/m^3) between 1 and 39 years (average of 10.5 years), continuously in the workplace	eye irritation		75%	ND	
			eye irritation		60%		
Holness and Nethercott, 1989, funeral services workers	84 exposed subjects	Average value of 0.36 ± 0.19 ppm, in the workplace	eye irritation		49% (N=67)	12% (N=17)	
			nose irritation		48% (N=67)	29% (N=17)	
			throat irritation		19% (N=67)	6% (N=17)	

ND: Not Determined

Study	Methodology				Confounding factors					Remarks
	Exposure evaluation	Evaluation of effects	Control group	Double blind	Room temperature	Level of humidity	Rate of air exchange	Wood dust	Other substances	
Alexandersson and Hedenstierna, 1988, paint (lacquer) industry workers	with portable equipment in the respiration zone, chemosorption method	Interview and questionnaires, spirometry	18 non exposed, of which 6 are smokers		measured but no published values	measured but no published values	ND	low	solvents (alcohol, BTX)	No obvious relationship between exposure to formaldehyde and the decrease in pulmonary function could be observed.
Alexandersson and Hedenstierna, 1989, wood industry workers		Questionnaire and spirometry	20 non exposed, of which 6 are smokers		21 - 22°C	31 - 33%	ND			Decrease in pulmonary function with exposure to formaldehyde. The effect appears to be cumulative over the years. Effects are reversible after 4 weeks without exposure.
Boysen et al., 1990, chemical plant worker	Subjective evaluation (no measures)	Questionnaire and culture and histological analysis of nasal cells	37 controls		not measured	not measured	no	probable	low	Specifically studies the appearance of dysplasia and metaplasia in exposed individuals as first sign of potential cancer.
Edling et al., 1987, wood industry workers	unspecified	Cytological testing and questionnaire	25 non-exposed subjects, of which 12 are smokers		ND	ND	ND	probable	probable	Histological changes in nasal mucosa in exposed individuals.
Holness and Nethercott, 1989, funeral services workers	chromotropic acid method	Clinical exam (dermatology), spirometry and questionnaire	38 controls		ND	ND		between 0.1 and 0.3 mg/m^3	traces of terpene	No significant difference in decrease of pulmonary function (FEF, FEV, FVC…)

ND: Not Determined

Study	Study Population	Exposure	Response				
			Measured effect	Severity of the effect	% of irritating effect response	% of response for controls	Time evolution
Horvath *et al*., 1988, (wood and farm-produce) industry workers	109 exposed subjects (number of healthy or sensitive individuals not specified), of which 53.2% are smokers and of which some of them live in mobile homes	Exposure to TWA between 0.17 and 2.93 ppm (avg. 0.69, median 0.62) for the unit of production of particle panels, continuous long-term exposure during work (activity)	Eye irritation		49.50%	24.0%	
			Nose and throat irritation		34.90%	13.0%	
			sore throat (dose-response relationship)		<.05ppm: 4%, 0.05-0.4ppm: 8%, 0,4-1.ppm: 21%, 1.0-3.0 ppm: 33%		
Nunn *et al.,* 1990, warehouse workers	125 subjects exposed to formaldehyde and other chemical substances, of which 58 are smokers	Exposure between 0.1 and >2 ppm	no studies of the irritating effects, study of respiratory function				
Ward *et al.,* autopsy and pathology service workers Ward et al., 1984	11 subjects, of which 2 are smokers	Average estimated exposure between 0.61 and 1.32 ppm	Study of sperm (number, morphology)				

ND: Not Determined

Study	Methodology				Confounding factors					Remarks
	Exposure evaluation	Evaluation of effects	Control group	Double blind	Room temperature	Level of humidity	Rate of air exchange	Wood dust	Other substances	
Horvath *et al*., 1988, (wood and farm-produce) industry workers	chromotropic acid spectrometric method	Questionnaire (before and after shift), spirometry	254 control subjects, of which 53.1% are smokers		23°C±1.5			between 0.25 and 4.40 mg/m^3	Carbon Monoxide	Significant decrease of FEV and FVC in the control group.
Nunn *et al*., 1990, warehouse workers.	evaluation quite subjective		95 non - exposed subjects, of which 43 are smokers						Various chemical products	No obvious correlation between exposure to formaldehyde and the decrease in pulmonary function could be observed.
Ward *et al*., 1984, autopsy and pathology service workers	measure in ambient air and respiratory zone	Sperm analysis	11 controls, of which 3 are smokers		ND	ND		No	probable, but not documented	No study on irritation. Study of sperm (number, morphology) which does not conclude in a difference between exposed and non- exposed individuals, probably due to lack of power.

ND: Not Determined

Table 2: Census of the number of subjects experiencing irritating effects to the eyes, nose and throat and perceiving odors according to the degree of exposure in the selected controlled studies

Number of subjects reporting eyes irritations according to the class of exposure and degree of severity

Conf. degree	Study	Severity of effects	Class of exposure					
			0 to <0.3 ppm	0.3 to <0.75 ppm	0.75 to <1 ppm	1 to <2 ppm	2 to <3 ppm	3 ppm and +
+	Sauder, 1987	none or mild	9					6
	N=9	moderate (tolerable or annoying)	0					3
		Severe	0					0
+	Sauder, 1987	none or mild	9					8
	N=9	moderate (tolerable or annoying)	0					1
		Severe	0					0
++	Weber-Tshopp, 1977	none or mild		32				28
	N=33	moderate (tolerable or annoying)		1				3
		Severe		0				2
++	Schachter, 1986	none or mild	15				12	
	N=15	moderate (tolerable or annoying)	0				2	
		Severe	0				1	
++	Schachter, 1987	none or mild	15				13	
	N=15	moderate (tolerable or annoying)	0				2	
		Severe	0				0	
++	Witek, 1987	none or mild	14				11	
	N=15	moderate (tolerable or annoying)	1				3	
		Severe	0				1	
+	Kulle, 1987	none or mild	15	15		13	13	10
	N=15	moderate (tolerable or annoying)	0	0		2	2	5
		Severe	0	0		0	0	0
+	Green, 1987	none or mild						29
	N=38	moderate (tolerable or annoying)						8
		Severe						1
+	Day, 1984	none or mild				16		
	N=18	moderate (tolerable or annoying)				2		
		Severe				0		
+	Bender, 1983	none or mild	28	45	5	24		
	N=variable	moderate (tolerable or annoying)	0	0	0	3		
		Severe	0	0	0	0		
+	Andersen, 1983	none or mild	16	16	14	14		
	N=16	moderate (tolerable or annoying)	0	0	2	2		
		Severe	0	0	0	0		

Note: The “Conf. degree” column represents the degree of confidence given to the study and it indicates the moderately high (“+”) or high (“++”) degree of confidence attributed to each study.

Number of subjects reporting nose irritations according to the class of exposure and degree of severity

Conf. degree	Study	Severity of effects	Class of exposure					
			0 to <0.3 ppm	0.3 to <0.75 ppm	0.75 to <1 ppm	1 to <2 ppm	2 to <3 ppm	3 ppm and +
+	Sauder, 1987	none or mild	9					6
	N=9	moderate (tolerable or annoying)	0					3
		Severe	0					0
+	Sauder, 1987	none or mild						4
	N=9	moderate (tolerable or annoying)						5
		Severe						0
++	Weber-Tshopp, 1977	none or mild						
	N=33	moderate (tolerable or annoying)						
		Severe						
++	Schachter, 1986	none or mild	15				14	
	N=15	moderate (tolerable or annoying)	0				1	
		Severe	0				0	
++	Schachter, 1987	none or mild	14				15	
	N=15	moderate (tolerable or annoying)	1				0	
		Severe	0				0	
++	Witek, 1987	none or mild	15				13	
	N=15	moderate (tolerable or annoying)	0				2	
		Severe	0				0	
+	Kulle, 1987	none or mild	15	15		15	13	14
	N=15	moderate (tolerable or annoying)	0	0		0	2	1
		Severe	0	0		0	0	0
+	Green, 1987	none or mild						26
	N=38	moderate (tolerable or annoying)						12
		Severe						0
+	Day, 1984	none or mild				17		
	N=18	moderate (tolerable or annoying)				1		
		Severe				0		
+	Bender, 1983	none or mild						
	N=variable	moderate (tolerable or annoying)						
		Severe						
+	Andersen, 1983	none or mild	16	16	14	14		
	N=16	moderate (tolerable or annoying)	0	0	2	2		
		Severe	0	0	0	0		

Note: The “Conf. degree” column represents the degree of confidence given to the study and it indicates the moderately high (“+”) or high (“++”) degree of confidence attributed to each study.

Number of subjects reporting throat irritations according to the class of exposure and degree of severity

Conf. degree	Study	Severity of effects	Class of exposure					
			0 to <0.3 ppm	0.3 to <0.75 ppm	0.75 to <1 ppm	1 to <2 ppm	2 to <3 ppm	3 ppm and +
+	Sauder, 1987	none or mild	9					6
	N=9	moderate (tolerable or annoying)	0					3
		Severe	0					0
+	Sauder, 1987	none or mild						4
	N=9	moderate (tolerable or annoying)						5
		Severe						0
++	Weber-Tshopp, 1977	none or mild						
	N=33	moderate (tolerable or annoying)						
		Severe						
++	Schachter, 1986	none or mild	15				15	
	N=15	moderate (tolerable or annoying)	0				0	
		Severe	0				0	
++	Schachter, 1987	none or mild	14				15	
	N=15	moderate (tolerable or annoying)	1				0	
		Severe	0				0	
++	Witek, 1987	none or mild	15				14	
	N=15	moderate (tolerable or annoying)	0				1	
		Severe	0				0	
+	Kulle, 1987	none or mild	15	15		15	13	14
	N=15	moderate (tolerable or annoying)	0	0		0	2	1
		Severe	0	0		0	0	0
+	Green, 1987	none or mild						26
	N=38	moderate (tolerable or annoying)						12
		Severe						0
+	Day, 1984	none or mild				17		
	N=18	moderate (tolerable or annoying)				1		
		Severe				0		
+	Bender, 1983	none or mild						
	N=variable	moderate (tolerable or annoying)						
		Severe						
+	Andersen, 1983	none or mild	16	16	14	14		
	N=16	moderate (tolerable or annoying)	0	0	2	2		
		Severe	0	0	0	0		

Note: The “Conf. degree” column represents the degree of confidence given to the study and it indicates the moderately high (“+”) or high (“++”) degree of confidence attributed to each study.

Number of subjects reporting odor perception according to the class of exposure and degree of severity

Conf. degree	Study	Severity of effects	Class of exposure					
			0 to <0.3 ppm	0.3 to <0.75 ppm	0.75 to <1 ppm	1 to <2 ppm	2 to <3 ppm	3 ppm and +
+	Sauder, 1987	none or mild						
	N=9	moderate (tolerable or annoying)						
		Severe						
+	Sauder, 1987	none or mild						7
	N=9	moderate (tolerable or annoying)						2
		Severe						0
++	Weber-Tshopp, 1977	none or mild						
	N=33	moderate (tolerable or annoying)						
		Severe						
++	Schachter, 1986	none or mild	15				9	
	N=15	moderate (tolerable or annoying)	0				6	
		Severe	0				0	
++	Schachter, 1987	none or mild	13				7	
	N=15	moderate (tolerable or annoying)	1				6	
		Severe	1				2	
++	Witek, 1987	none or mild	14				3	
	N=15	moderate (tolerable or annoying)	0				9	
		Severe	1				3	
+	Kulle, 1987	none or mild	15				11	
	N=15	moderate (tolerable or annoying)	0				4	
		Severe	0				0	
+	Green, 1987	none or mild						28
	N=38	moderate (tolerable or annoying)						10
		Severe						0
+	Day, 1984	none or mild						
	N=18	moderate (tolerable or annoying)						
		Severe						
+	Bender, 1983	none or mild						
	N=variable	moderate (tolerable or annoying)						
		Severe						
+	Andersen, 1983	none or mild						
	N=16	moderate (tolerable or annoying)						
		Severe						

Note: The “Conf. degree” column represents the degree of confidence given to the study and it indicates the moderately high (“+”) or high (“++”) degree of confidence attributed to each study.

Table 3: Number and percentage of workers experiencing irritating effects in studies performed in the workplace according to the degree of exposure

			Horvath *et al.* (1988)		Edling *et al.* (1987)		Holness & Nethercott (1989)		Alexandersson & Hedenstierna (1989)		Alexandersson & Hedenstierna (1988)	
Effect			Controls	Exposed	Controls	Exposed	Controls	Exposed	Controls	Exposed	Controls	Exposed
Eye irritation	Yes	N	193	55		19	30	49	19	8	17	28
		%	76%	50%		25%	79%	58%	59%	38%	94%	74%
	No	N	61	54		56	8	35	13	13	1	10
		%	24%	50%		75%	21%	42%	41%	62%	6%	26%
	Sum	N	254	109		75	38	84	32	21	18	38
		%	100%	100%		100%	100%	100%	100%	100%	100%	100%
Nasal irritation	Yes	N	221	71		30	32	47	25	15	18	32
		%	87%	65%		40%	84%	56%	78%	71%	100%	84%
	No	N	33	38		45	6	37	7	6	0	6
		%	13%	35%		60%	16%	44%	22%	29%	0%	16%
	Sum	N	254	109		75	38	84	32	21	18	38
		%	100%	100%		100%	100%	100%	100%	100%	100%	100%
Throat irritation	Yes	N	221	71			36	70			18	32
		%	87%	65%			95%	83%			100%	84%
	No	N	33	38			2	14			0	6
		%	13%	35%			5%	17%			0%	16%
	Sum	N	254	109			38	84			18	38
		%	100%	100%			100%	100%			100%	100%
Exposure data (ppm)		Average		0.69				0.36				0.32
		Median		0.62								
		Standard deviation						0.19				
		Range		0.17-2.93		0.08-0.88				0.34-0.4		0.11-2.1
		Peaks				4						avg. 0.56

5.1.2 Determination the dose-response relationship based on data available in literature

The global dose-response relationship was determined based on data in Table 2. The results are presented in Table 4.

Table 4: Number of subjects and proportion (%) experiencing irritating effects on the eyes, nose and throat following of an acute exposure to various concentrations of formaldehyde, based on all data of controlled studies available in literature

			Exposure (ppm)						
Nature of effect	Severity		0 - <0.3	0.3 - <0.75	0.75 - <1	1 - <2	2 - <3	≥3	Total
Eye irritation	No effect or mild effect	Number (N)	121	108	19	67	49	81	445
		Proportion (%)	99.2%	99.1%	90.5%	88.2%	81.7%	77.9%	90.4%
	Moderate effect (tolerable or annoying)	Number (N)	1	1	2	9	9	20	42
		Proportion (%)	0.8%	0.9%	9.5%	11.8%	15.0%	19.2%	8.5%
	Severe effect	Number (N)	0	0	0	0	2	3	5
		Proportion (%)	0.0%	0.0%	0.0%	0.0%	3.3%	2.9%	1.0%
	Total	Number (N)	122	109	21	76	60	104	492
		Proportion (%)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Nose irritation	No effect or mild effect	Number (N)	83	31	14	46	55	50	279
		Proportion (%)	97.6%	100.0%	87.5%	93.9%	91.7%	70.4%	89.4%
	Moderate effect (tolerable or annoying)	Number (N)	2	0	2	3	5	21	33
		Proportion (%)	2.4%	0.0%	12.5%	6.1%	8.3%	29.6%	10.6%
	Severe effect	Number (N)	0	0	0	0	0	0	0
		Proportion (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Total	Number (N)	85	31	16	49	60	71	312
		Proportion (%)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Throat irritation	No effect or mild effect	Number (N)	84	31	14	46	57	50	282
		Proportion (%)	98.8%	100.0%	87.5%	93.9%	95.0%	70.4%	90.4%
	Moderate effect (tolerable or annoying)	Number (N)	1	0	2	3	3	21	30
		Proportion (%)	1.2%	0.0%	12.5%	6.1%	5.0%	29.6%	9.6%
	Severe effect	Number (N)	0	0	0	0	0	0	0
		Proportion (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Total	Number (N)	85	31	16	49	60	71	312
		Proportion (%)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Perception of odor	No effect or mild effect	Number (N)	57	ND	ND	ND	30	35	122
		Proportion (%)	95.0%	ND	ND	ND	50.0%	74.5%	73.1%
	Moderate effect (tolerable or annoying)	Number (N)	1	ND	ND	ND	25	12	38
		Proportion (%)	1.7%	ND	ND	ND	41.7%	25.5%	22.8%
	Severe effect	Number (N)	2	ND	ND	ND	5	ND	7
		Proportion (%)	3.3%	ND	ND	ND	8.3%	ND	4.2%
	Total	Number (N)	60	ND	ND	ND	60	47	167
		Proportion (%)	100.0%	ND	ND	ND	100.0%	100.0%	100.0%

ND: not determined
The "≥3" class represents the subjects exposed to between 3 and 4 ppm.

The analysis of Table 4 points out:

- a reduction in the proportion of individuals not experiencing any effect or a mild effect when the formaldehyde concentration increases over 0.75 ppm;

- an increase in the proportion of individuals experiencing a (moderate or severe) effect when the formaldehyde concentration increases over 0.75 ppm;

- the two previous phenomena show the existence of an exposure-response relationship for the irritating effects in the presence of formaldehyde;

- the quantity of data concerning the perception of odor and the measurement subjectivity for this parameter are the reasons why this effect was not selected for follow-up.

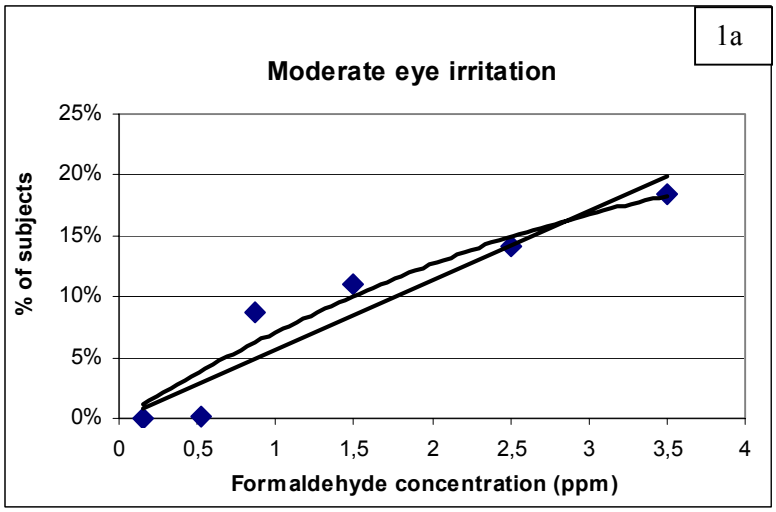
Nevertheless, it is worth mentioning that in the "moderate effects" category, which includes both the tolerable moderate effects and the annoying moderate effects, the effects reported in literature in the context of controlled studies for concentrations up to 3 ppm, are for the majority more tolerable than annoying. In addition, it was observed that severe effects appear at higher concentrations than moderate effects do, which was predictable. These effects manifest themselves only in the eyes, at concentrations lower than 3 ppm, and in very low proportions. They do not appear for the nose and throat at these concentrations. Moreover, the concentrations for the appearance of effects are in agreement with the NOAEL and LOAEL for humans determined in various studies and presented in Appendix 1.

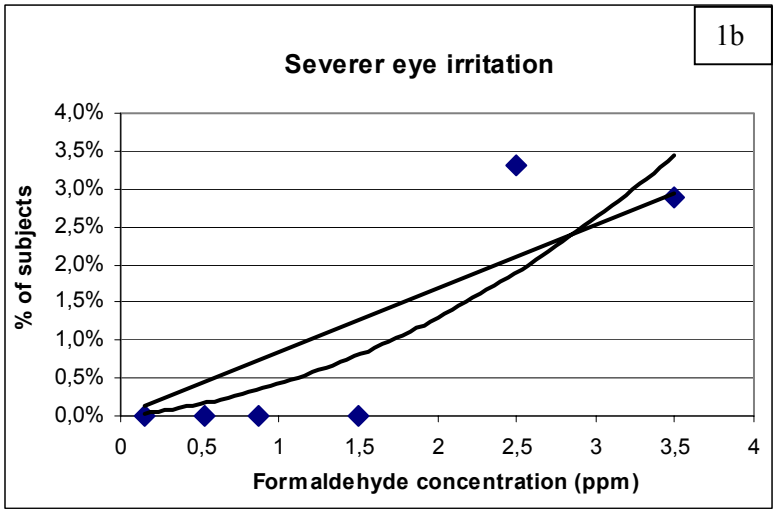
Based on the data presented in Table 4, the mathematical models of the dose-response relationship, i.e. linear and and polynomial curves of degree 2 to 4, were derived for eye, nose and throat irritation after the background noise values had been substracted (Class 0 - <0.3 ppm). Figure 1 shows the optimum statistical adjustment for the linear regression model and the polynomial regression model of degree 2 (or, in other words, quadratic regressions) to the data in Table 4. Table 5 shows the equations for linear and quadratic regressions, as well as the correlation coefficients obtained following these adjustments. The degree 3 and 4 polynomial regressions were not selected since the results did not show any correspondence to reality.

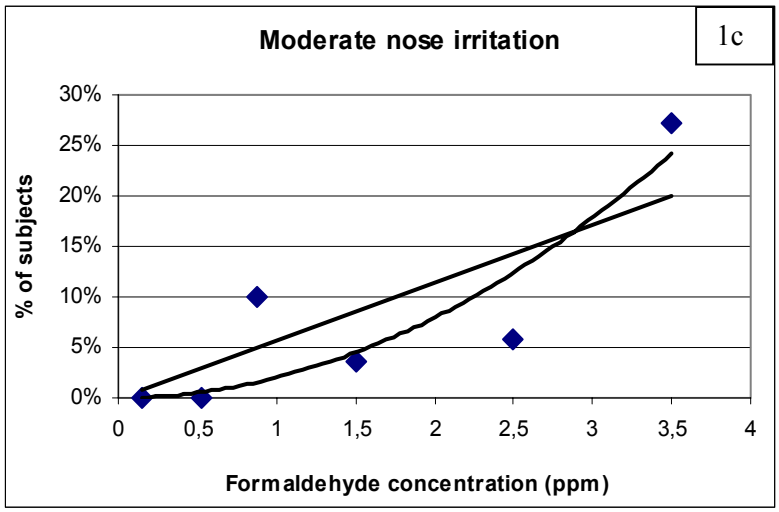
Table 5: Equations of linear and quadratic mathematical models adjusted to the experimental data for the determination of the dose-response relationship

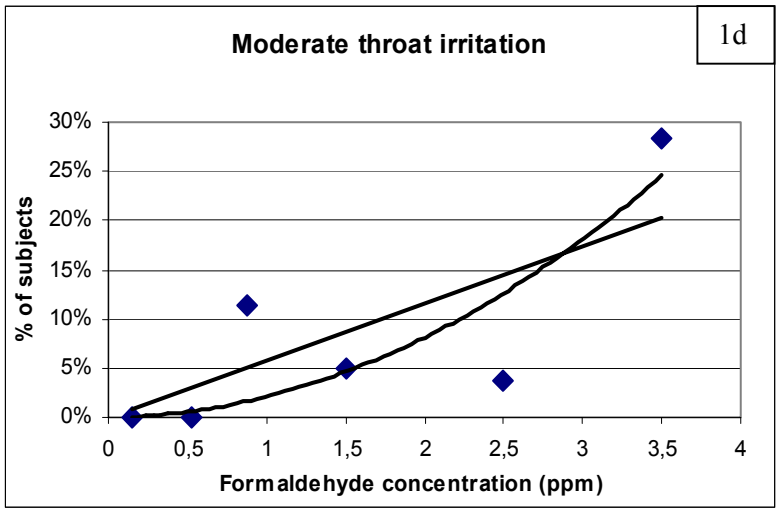
Effect considered	Type of regression	Equations	Correlation coefficients
Eyes - Moderate	Linear	$y = 0.0569x$	$R^2 = 0.8880$
	Quadratic	$y = -0.0075x^2 + 0.0784x$	$R^2 = 0.9174$
Eyes - Severe	Linear	$y = 0.0084x$	$R^2 = 0.7069$
	Quadratic	$y = 0.0022x^2 + 0.002x$	$R^2 = 0.7633$
Nose - Moderate	Linear	$y = 0.057x$	$R^2 = 0.6532$
	Quadratic	$y = 0.0196x^2 + 0.0006x$	$R^2 = 0.7611$
Throat - Moderate	Linear	$y = 0.0578x$	$R^2 = 0.5821$
	Quadratic	$y = 0.0196x^2 + 0.0014x$	$R^2 = 0.6793$

Figure 1: Curves of linear and quadratic dose-response relationships representing the percentage of the population experiencing irritating effects attributable to the exposure to formaldehyde




1b
Severer eye irritation
4,0%
3,5%
3,0%
2,5%
2,0%
1,5%
1,0%
0,5%
0,0%
% of subjects
0
0,5
1
1,5
2
2,5
3
3,5
4
Formaldehyde concentration (ppm)


1c
Moderate nose irritation
30%
25%
20%
15%
10%
5%
0%
% of subjects
0
0,5
1
1,5
2
2,5
3
3,5
4
Formaldehyde concentration (ppm)


1d
Moderate throat irritation
30%
25%
20%
15%
10%
5%
0%
% of subjects
0
0,5
1
1,5
2
2,5
3
3,5
4
Formaldehyde concentration (ppm)

These four graphs show that the degree 2 polynomial regression equations (i.e. quadratic regression) present a better adjustment to the experimental points and the correlation coefficients of quadratic regressions are better than those of linear regressions. Therefore, the quadratic regression was considered the most appropriate to describe the dose-response relationship that exists between the exposure to formaldehyde and the appearance of irritating effects. The moderate eye irritation presents the best correlation coefficient, followed by the severe eye irritation, then by the moderate nose and throat irritation. Therefore, the moderate eye irritation seems to be the most sensitive and the most precise effect to reflect the condition of the population.

The quadratic regression equations determined statistically from best-fits to the experimental points of the analysis of all the studies selected from the literature made it possible to estimate the theoretical percentage of people susceptible to experiencing an irritating effect depending on targeted concentrations in the context of lowering the standard (Table 6 and Figure 2). The experimental data showed that there is no difference between the proportion of symptoms exhibited by the control subjects without occupational exposure and individuals exposed to formaldehyde concentrations of less than 0.75 ppm. For these classes of exposure (0 - <0.3 and 0.3 - <0.75 ppm), the response percentage attributable to formaldehyde exposure was considered to be zero for the moderate effects on the eyes, nose and throat. For the severe effects on the eyes, the response percentage is also negligible for the 0.75 - <1.0 ppm class.

Although the quadratic model was used to establish the dose-response relationship, it was observed that, whatever the model selected, there is little difference in the estimate of the proportions of people susceptible to experiencing irritating effects.

Table 6, the data of which are also represented in Figure 2, indicates that the workers exposed to formaldehyde concentrations of less than 0.75 ppm should not experience any moderate or severe irritating eye, nose or throat effects. 6.3% of the workers exposed to a formaldehyde concentration between 0.75 and <1.0 ppm are likely to experience moderate eye irritation; none of them is likely to experience severe eye irritation and 1.6% of them may experience moderate nose and throat irritation. The corresponding values for the workers exposed to a formaldehyde concentration between 1 and <2.0 ppm are 10.1%, 0.8%, and ≈4.5%, as well as 14.9%, 1.9%, and ≈12.5%, respectively, for the workers exposed to 2 to <3 ppm (≥2 ppm).

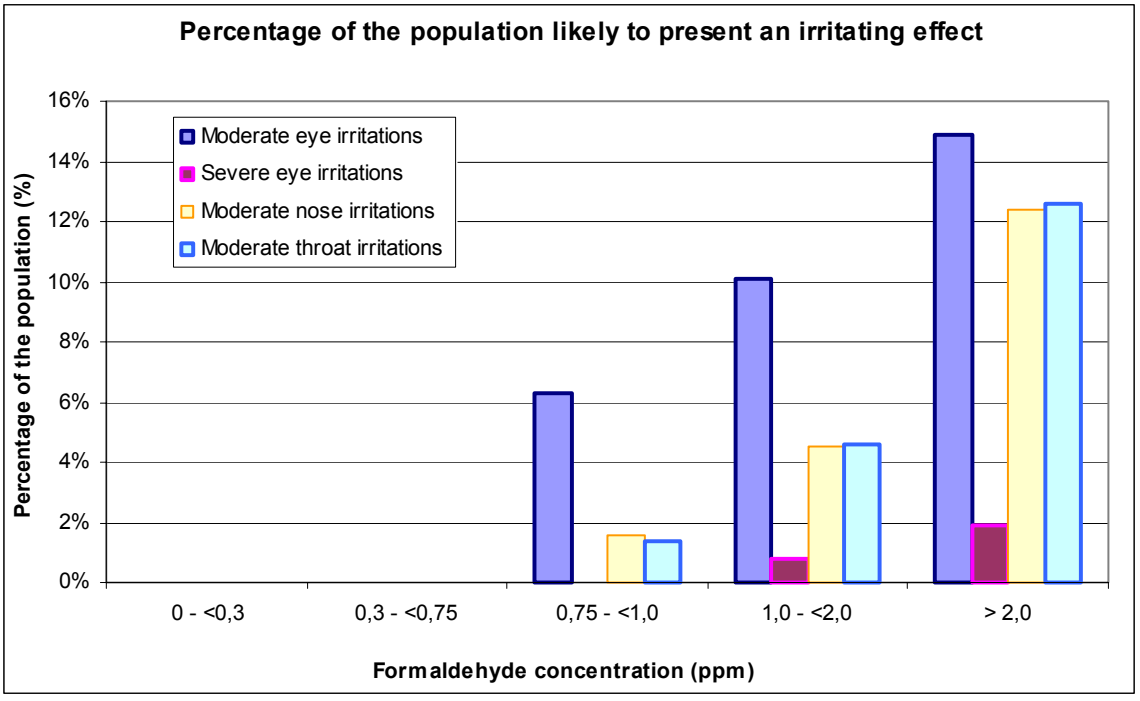
Table 6: Average theoretical percentage of the exposed population that is likely to experience irritating eye, nose or throat effects, attributable exclusively to formaldehyde, according to the severity of the effect, for a given class of exposure

Effect considered	Fraction of the population exposed (in %) experiencing irritating effects				
	0 - <0.3 ppm	0.3 - <0.75 ppm	0.75 - <1.0 ppm*	1 - <2.0 ppm*	≥2.0 ppm*
Eye irritation Moderate effect	0%	0%	6.3%	10.1%	14.9%
Eye irritation Severe effect	0%	0%	0%	0.8%	1.9%
Nose irritation Moderate effect	0%	0%	1.6%	4.5%	12.4%
Throat irritation Moderate effect	0%	0%	1.6%	4.6%	12.6%

* The values of these classes were calculated for the middle of the classes of exposure, based on quadratic regression models from which the background noise had been subtracted.

Note: The ≥2.0 ppm class represents the individuals exposed between 2.0 and <3.0 ppm

Figure 2: Average theoretical percentage of the exposed population that is likely to experience irritating eye, nose or throat effects, attributable exclusively to formaldehyde, according to the severity of the effect, for a given class of exposure



5.1.3 Application of the dose-response relationship to the data on exposure to formaldehyde in various industrial sectors in Quebec

The results concerning this section can be found in the main report. In addition, the specific results by industrial sector can be found individually in the various sectional annexes. Please refer to them.

5.1.4 Determination of the impact on health of lowering the standard to 1.0, 0.75, or 0.3 ppm

The results concerning this section can be found in the main report. In addition, the specific results by industrial area can be found individually in the various sectional annexes. Please refer to them.

5.2 Effects due to subacute to subchronic exposure

There are some studies performed in a controlled environment and other studies performed in the workplace, which aimed to assess the health effects of formaldehyde as a result of a subacute to subchronic exposure.

Certain studies were performed in a controlled environment on healthy or asthmatic subjects, without documented occupational exposure, in order to verify a possible association between acute or subacute exposure to formaldehyde vapors and the reduction of pulmonary function or the onset of asthma attacks (8, 10, 12, 13, 56-59). The majority of these studies did not notice any significant change in the pulmonary function, the bronchial reactivity or bronchoconstriction for exposure concentration of up to 2 or 3 ppm (10, 12, 56-59). However, Sauder *et al*. (13) observed a transitory reduction in the pulmonary function after acute exposure to 3 ppm in healthy subjects. Green *et al*. (8) observed a statistically significant reduction in the pulmonary function in non-asthmatic individuals exposed to 3 ppm, while the asthmatic subjects exposed to 3 ppm did not experience any reduction in the pulmonary function.

Certain studies in a controlled environment were also performed on subjects occupationally exposed to formaldehyde in order to verify the appearance of these symptoms as a result of acute or subacute exposure to formaldehyde vapors in an inhalation chamber (11, 16, 17, 60). In the studies performed by Schachter *et al*. (60) and by Reed and Frigas (11), no alteration of the pulmonary function, no lower respiratory tract symptoms and no asthma attacks were observed for exposure concentrations of up to 2 or 3 ppm. However, in the study performed by Nordman *et al*. (17) on 230 workers known to exhibit asthmatic type respiratory symptoms, an acute exposure to formaldehyde vapors in an inhalation chamber triggered asthma attacks in 11 of the subjects exposed to 2 ppm and only one subject reacted at 1 ppm. Moreover, Lemiere *et al*. (16) reported the cases of 3 workers who developed asthmatic reactions following occupational exposure. Evaluations were performed on these subjects in a clinical environment, in an inhalation chamber. In a first phase, they were exposed to resin particles containing various chemical substances (phenol, amine, formaldehyde in unknown concentrations), and the three subjects experienced alterations of pulmonary function and asthmatic reactions. In a second phase, they were exposed only to gaseous formaldehyde in concentrations of up to 2 ppm, and no reaction was observed in two of the subjects, while the

third one had an asthmatic-type reaction. In all cases, stopping the exposure made it possible to regain an asymptomatic condition.

Several studies were also performed in the workplace in order to evaluate the alteration of the pulmonary function in individuals exposed to formaldehyde (9, 18, 19, 61). The Alexandersson and Hedenstierna study (18) showed a significant reduction only of the forced vital capacity and the forced expiratory volume in 1 second, but not of the other pulmonary functions when the workers were exposed to approximately 0.5 ppm of formaldehyde. A similar study performed by the same authors (19) also showed a significant reduction in the pulmonary function of workers exposed daily for several years to approximately 0.5 ppm of formaldehyde. However, this reduction proved to be reversible and the subjects entirely recovered their pulmonary function after four weeks without exposure. However, it is important to note that these studies were performed in industries that use numerous other possibly irritating chemical products (paint and varnish industry, [18]) and that sawdust was also present (19). Therefore, the presence of uncontrolled confounding factors does not make it possible to incriminate formaldehyde with certainty as being the causal agent of this effect. On the contrary, the other studies also performed in the workplace (61) did not show a reduction in the respiratory function of the workers exposed to formaldehyde concentrations of up to 2.0 ppm. In the study performed by Holness and Nethercott (9), 4% of the 84 workers reacted positively to skin tests specific for formaldehyde, but these results do not make it possible to conclude in a response induced by respiratory exposure in the workplace.

5.3 Results concerning the effects due to chronic exposure

5.3.1 Evaluation of epidemiological studies

In order to evaluate the risk of cancer associated with formaldehyde exposure in the workplace, the epidemiological studies (cohort, case-control, meta-analysis) dealing with this subject were revised, selected based on pre-established criteria, and analyzed. The detailed analysis of these studies and the results are given in Appendix 2.

5.3.1.1 Case-control studies

Cancers of the sinuses and of nasal cavities were evaluated in half of the studies selected, i.e. in nine studies out of 18. Two of these studies (62, 63) showed negative results (OR of 0.3 and 0.4 respectively), i.e. a tendency toward a protective effect of formaldehyde, but not statistically significant. Two other studies (30, 64) showed positive results (OR of 1.5 and 2.5, respectively), but also not statistically significant. In one study (65), a statistically significant risk was obtained (OR: 2.5; CI90%: 1.5-4.3); however, the authors used a confidence interval of 90% instead of 95%. Four studies reported a statistically significant risk in one or several of their subdivisions. In the first of the four studies (20), a significant risk was obtained in men (OR: 2.8; CI95%: 1.8-4.3) and also in men exposed to fine sawdust (OR: 3.5; CI95%: 2.2-5.6). In the other three studies, where squamous cell carcinoma and adenocarcinoma of the sinuses and nasal cavities were evaluated separately (22, 23, 66), the tendency was the same, i.e. no risk increase was observed for squamous cell carcinoma, but there was a presence of risk increase for adenocarcinoma. Among these three studies, the first study (66) reported a largely significant risk of adenocarcinoma in men exposed to average and high levels (OR: 5.33; CI95%: 1.28-22.20), in men exposed for a period of more than 20 years (OR: 6.86; CI95%: 1.69-27.80) and in men with high cumulative exposure (OR:

6.91; CI95%: 1.69-28.23). For the last two observations, the very high confidence intervals reflect a significant lack of power that reduces accuracy and consequently the significance of the conclusions on the observed OR. The second study (22) reported a significant risk of adenocarcinoma (OR: 3.30; CI95%: 1.98-5.49), as well as a significant risk (OR: 1.66; CI95%: 1.27-2.17) in men (adenocarcinoma and squamous cell carcinoma combined). The last of the three studies (23) reported a significant risk of adenocarcinoma in men exposed to average concentrations of formaldehyde (OR: 2.4; CI95%: 1.3-4.5), in men exposed to high concentrations (OR: 3.0; CI95%: 1.5-5.7), and in women exposed to high concentrations (OR: 6.2; CI95%: 2.0-19.7). It should be noted that the last two studies (22, 23) were combined studies (meta-analysis) of 8 and 12 studies respectively, and that they include the second study (66). Almost 50% of the cases reported in the combined studies come from this second study; therefore, it is normal to notice a similarity among these three studies.

Concerning certain cancers of the oral cavity and the pharynx, the evaluation was performed in eleven studies (20, 28, 31, 32, 37, 63, 64, 67-70). When cancers of the oral cavity and the pharynx were evaluated globally, a risk that was not statistically significant (OR of 1.3 and 1.8, respectively) was observed (37, 70). The evaluation of the pharynx alone (70) as well as the oropharynx and the hypopharynx (63) did not make it possible to show the presence of an increased risk (OR of 1.01 and OR of 0.6 and 1.5, respectively). However, in a study that evaluated the squamous cell carcinoma of the hypopharynx (28), a statistically significant risk (OR: 3.78; CI95%: 1.50-9.49) was obtained in individuals in whom the probability of exposure was more than 50%. Nasopharyngeal cancer was evaluated separately in eight control case studies. Four of these eight studies (20, 63, 64, 69) did not observe any statistically significant results (OR values of 0.7 through 2.6, depending on the studies). The other four studies (30-32, 68) reported a statistically significant risk under various conditions: 1) in individuals probably exposed to high levels for more than 20 years prior to death, and deceased at the age of more than 68 years old (OR: 4.0; bilateral, $p = 0.015$) (30); 2) in workers exposed for less than 15 years (OR: 2.7; CI95%: 1.1-6.6), in those for whom over 25 years had passed since the first exposure (OR: 2.9; CI95%: 1.1-7.6), and also in those who were younger than 25 when the first exposure occurred (OR: 2.7; CI95%: 1.1-6.6) (31); 3) in workers with the highest cumulative exposure (OR: 3.0; CI95%: 1.3-6.6) (68); 4) in workers exposed and EBV virus positive (OR: 2.7; CI95%: 1.2-5.9) (32).

Cancer of the larynx was also evaluated in three studies (28, 36, 37). None of these studies reported a statistically significant risk (OR values of 0.9 through 4.3, depending on the studies), except one study for which a largely significant risk was obtained in strongly exposed individuals for a period of 10 years or more (OR: 4.3; CI95%: 1.0-18.7) (36), but with lack of power, reducing the accuracy and limiting the conclusions that can be drawn. Finally, in one study (67) that globally evaluated the upper respiratory tract, a risk that is not significant statistically was observed (OR: 2.38; CI90%: 0.43-13.2).

Based on the results obtained in the control case studies, it is difficult to conclude with a good degree of confidence that formaldehyde can cause cancer of the sinuses and nasal cavities, of the oral cavity, the pharynx or the larynx in humans. The results do not always agree among the various studies. Actually, there is sometimes a certain relationship with the duration of exposure, while in other studies there is a relationship with cumulative exposure, the duration since the first exposure or with the average exposure levels. According to these studies, there is absolutely no general tendency. Another major limitation of these studies is the lack of observable power based on confidence intervals obtained on the calculated ORs.

Several other limitations were observed by the authors, such as the presence of potential uncontrolled confounding factors, or limitations in evaluation of the exposure.

5.3.1.2 Analysis of cohort studies

Cancer of the sinuses and nasal cavities was studied in nine studies (24, 25, 29, 34, 38, 42, 71-73). However, given the rarity of this type of cancer, five studies (38, 42, 71-73) do not report any cases of cancer, while the expected number, when indicated, varied between 0.5 and 1.7. When cases were observed (24, 34), the number observed was always lower than the expected number according to sanitary data of the general population, i.e. respectively 1 instead of 1.7 and 2 instead of 2.2. Another study (29) obtained a risk that was not statistically significant (SMR: 381) where only 2 cases were observed. Finally, a last study (25) observed a statistically significant risk in individuals exposed to formaldehyde (SPIR: 2.3; CI95%: 1.3-4.0), and in workers exposed to formaldehyde but not exposed to fine sawdust (SPIR: 3.0; CI95%: 1.4-5.7).

Cancer of the oral cavity and the pharynx was studied in nine cohort studies (24, 25, 29, 34, 38, 42, 71-73). Only one study (29) observed a statistically significant increase in cancer (SMR: 229; $p \leq 0.05$), among short-term employees (employees for less than a year) hired between 1947 and 1956. The other studies obtained a risk measure that was not statistically significant between 28 and 201. Two studies (29, 38) evaluated the oral cavity separately. The first study (29) obtained a risk that was not statistically significant (SMR: 131), but the second study (38) obtained a significant increase (SMR: 343; CI90%: 118-786), however, the authors used a confidence interval of 90%. They also obtained a statistically significant risk in workers exposed for more than 10 years (SMR: 757; $p<0.01$). When the cancer of the pharynx (34, 38) was evaluated separately, a risk that was not statistically significant was reported (SMR of 113 and 147, respectively). Twelve studies (24, 25, 29, 33, 34, 38, 42, 71-74) also evaluated cancer of the nasopharynx separately. However, given the rarity of this type of cancer, five studies (34, 38, 71-73) did not observe any cases. Only one of these studies (34) reported the number of expected cases, i.e. 1.3, and three studies (24, 29, 33) obtained a statistically significant risk for workers 1) exposed only to formaldehyde (SMR: 270; $p \leq 0.05$) (24); 2) exposed to formaldehyde and to particles (SMR: 388; $p \leq 0.05$) (33), which included those with the highest cumulative exposure to formaldehyde (SMR: 826; $p \leq 0.05$), short-term employees (SMR: 517; $p \leq 0.05$), as well as a particularly significant risk in individuals exposed to formaldehyde and particles in one of the installations (SMR: 1026; $p \leq 0.01$); 3) exposed to formaldehyde (SMR: 533; $p \leq 0.05$) and particularly in workers with long-term exposure (more than a year) hired between 1947 and 1956 (SMR: 1049; $p \leq 0.05$) (29). Three studies (25, 42, 74) obtained a risk measure that was not statistically significant between 130 and 746. Cancer of the oropharynx was also evaluated separately in three studies (24, 29, 74). One study (24) obtained a statistically significant risk (SMR: 443; $p \leq 0.05$) in workers exposed to 0.5 ppm year or less of formaldehyde, while the other two studies obtained risk increases that were not significant (SMR of 184 and 457, respectively) (29, 74). In certain exposure categories, no cases were observed (less than 1 case was expected). Two studies (24, 29) evaluated cancer of the hypopharynx separately and obtained an increase that was not significant (SMR of 141 and 594, respectively). Cancer of the larynx was also evaluated in eight studies (24, 25, 29, 34, 42, 71-73), but none of them observed any statistically significant risk; the measure of the risk obtained varied between 39 and 292.

Based on the results obtained in the cohort-type studies, it is difficult to conclude with a good degree of confidence that formaldehyde can cause cancer of the sinuses and nasal cavities, of the oral cavity, and the pharynx. The results do not always agree among the various studies. Actually, there is sometimes a certain relationship with the duration of exposure, while in other studies there is a relationship with cumulative exposure. There is definitely no tendency resulting from these studies. However, it is interesting to notice that six of the 12 studies that evaluated nasopharyngeal cancer obtained a risk in connection with the exposure to formaldehyde, generally rather significant (SMR ≈ 400), but not always statistically significant. The other six studies did not notice any cases. Since few studies obtained a significant risk and given the presence of methodological limitations observed in most of these studies, the main one being the lack of power due to the rarity of these types of cancer, it is not possible to clearly conclude that formaldehyde can cause nasopharyngeal cancer. In addition, the risk is not always observed in the highest exposure categories; a high risk is sometimes exhibited in workers that fall in the lowest exposure category, which is the opposite of what is expected. A causal association cannot be entirely excluded, nor can the absence of association.

5.3.1.3 Analysis of meta-analyses

The three meta-analyses (26, 27, 35) evaluated cancer of the sinuses and the nasal cavities. The first study (35) did not observe any risk (OR of 0.4 and 1.1, respectively). The second study (26) observed a significant risk (RR: 1.75; CI95%: 1.21-2.43) in workers with high level or duration of exposure. In the last study (27), the authors stratified by type of study, and a significant risk was observed when only the case-control studies were evaluated (mRR: 1.8; CI95%: 1.4-2.3), and when the European studies were evaluated separately (mRR: 2.9; CI95%: 2.2-4.0), where there are generally more significant levels of fine sawdust. However, the authors observed a statistically significant reduction when they stratified the cohort studies (mRR: 0.3; CI95%: 0.1-0.9).

One study (35) globally evaluated cancer of the oral cavity and the pharynx and did not observe any risk (OR: 1.0). The three meta-analysis type studies evaluated nasopharyngeal cancer separately. The first two studies (26, 35) obtained a statistically significant risk (OR: 2.1; $p \leq 0.05$ and 2.59; CI95%: 1.29-5.36, respectively) in individuals with a high level or duration of exposure. The third study (27) obtained a statistically significant risk (mRR: 1.3; CI95%: 1.2-1.5) in workers exposed to formaldehyde when all the studies (case-control and cohort) were included in the analysis. One of the meta-analysis type studies (26) evaluated cancer of other sites of the oral cavity and the pharynx (oropharynx, hypopharynx, lip, tongue, salivary glands and mouth) and observed a risk that was not significant (OR: 1.16) in workers with a high level or duration of exposure.

Based on the results obtained in the meta-analysis type studies, it is not possible to conclude with a good degree of confidence that formaldehyde can cause cancer of the sinuses and nasal cavities, of the oral cavity, and the pharynx, when they are evaluated globally. However, there seems to be a risk of nasopharyngeal cancer, demonstrated in the three studies when it is evaluated separately. In all cases, whatever the type of cancer considered, the results are based on a low number of meta-analyses and these comprise mostly the same epidemiological studies, which limits the force of the association and calls for cautious interpretation of the consistency among these three studies.

In summary, the results of the analysis of all of the epidemiological studies described above are not consistent enough to constitute sufficient proof of a causal association between formaldehyde exposure and the appearance of cancer. However, it is possible to conclude limited proof. In addition, in numerous studies, the level of exposure is not precisely established, or it is based on sporadic measurements. Therefore, it is not possible to establish, based on the epidemiological studies, a dose-response relationship between formaldehyde exposure and the appearance of cancer in the concentration range of the VEA. Based mainly on the animal data available, two organizations, the U.S. EPA (51) and the CIIT (75), have however established a dose-response relationship in order to quantify the risk of cancer. The data were issued from animal groups that experienced an excess of cancer when exposed to very high concentrations—concentrations for which the irritating effects were necessarily present—and being capable of causing a promoting effect and increase the risk of cancer. Tissue irritation could indeed cause cell death and induce an inflammatory response and tissue repair. Cell multiplication that would have suffered a mutation in this tissue at a higher rate than normal could increase the probability of failure to repair the affected DNA and therefore promote an increase in the risk of cancer if the unpaired mutation has carcinogenic properties. We must remember that the repair mechanism for mutated DNA is a saturable enzymatic mechanism.

5.3.2 Quantification of the risk of cancer associated with exposure to formaldehyde

5.3.2.1 U.S. EPA Evaluation

Based on animal data, the U.S. EPA suggested in 1987 an excess unit risk coefficient for formaldehyde inhalation (inhalation unit risk) of 1.3×10^{-5} $(\mu g/m^{3)-1}$ or 1.60×10^{-2} ppm^{-1} (knowing that 1 mg/m^3 equals 0.81 ppm). This coefficient was obtained by performing a procedure of linearization of the multi-stage model with an excess risk expressed in an additive pattern. The data at the basis of this excess unit risk coefficient for inhalation were the data relative to F-344 male rats in the Kerns *et al*. study (76) concerning carcinomas of squamous cells of the nose, and the dose scale used was the one for the environmental concentration to which the animals were exposed.

Nevertheless, in 1991, the U.S. EPA revised its position (52). In this revision, the U.S. EPA suggested, among other things, to not consider the environmental concentrations as dose scale, but to favor the data relative to DNA-formaldehyde/formaldehyde-proteins binding as "substitute for the concentrations delivered to target cells," and recommended the usage of the data on Rhesus monkeys and F-344 rats from the Casanova *et al*. study (77) in order to take into consideration the impact of the morphology of the upper respiratory tract in extrapolations from rat to monkey and to be closer to humans (78). In 1991, on the basis of these works, the U.S. EPA proposed in this way a revised excess unit risk coefficient for formaldehyde inhalation (inhalation unit risk) of 2.7×10^{-7} $(\mu g/m^{3)-1}$ or 3.3×10^{-4} ppm^{-1} (52, 53).

5.3.2.2 CIIT Evaluation

The CIIT (75) also tried to quantify the risk of cancer associated with formaldehyde exposure. This quantification is based on animal data, and on a two-stage carcinogenesis model, consisting of the direct mutagenic effect (binding to the DNA) and the cytotoxic potential of formaldehyde involving the proliferation of regenerative cells after cell death. It should be noted that this is the only cancer risk evaluation model to have been validated with epidemiological data for which a statistical association had been observed. Model parameters were determined taking into consideration the adjustment of these epidemiological data. Thus, on this basis, the CIIT proposes several values of excess risk of cancer of the respiratory tract, depending on whether the exposure is environmental or occupational, and whether the subjects were smokers or non-smokers.

Table 7: CIIT prediction for excess risk of cancer of the respiratory tract due to occupational exposure to formaldehyde

Formaldehyde concentration (ppm)	Prediction of excess risk of cancer		
	Non-smoker	Mixed (smoker and non-smoker)	Smoker
0.1 ppm	4.1×10^{-9}	7.6×10^{-8}	1.0×10^{-7}
0.3 ppm	1.3×10^{-8}	2.6×10^{-7}	3.8×10^{-7}
0.5 ppm	2.5×10^{-8}	5.0×10^{-7}	7.2×10^{-7}
0.7 ppm	3.4×10^{-7}	8.0×10^{-6}	6.6×10^{-6}
1.0 ppm	8.8×10^{-6}	2.1×10^{-4}	1.5×10^{-4}

The application of these values to the Quebec context (that is to say, the number of industrial workers who were possibly exposed to formaldehyde) and the interpretation of these results are given in the main report.

6 DISCUSSION

6.1 Effects due to acute exposure

6.1.1 Determination of the dose-response relationship based on data available in literature

6.1.1.1 Advantages and limitations of the approach used

The approach adopted to establish the dose-response relationship had the following characteristics:

1. The relationship between formaldehyde exposure and the appearance of the most sensitive and early effects was established, i.e. the eye, nose and throat irritating effects. Eye irritation seems to be the most sensitive irritating effect (60, 79) and it would be a pertinent choice if only one of these various irritating effects were to be considered. The eye irritating effects exhibit all of the following characteristics:

   - very early effect, very sensitive and it seems to be representative of the reality;
   - effect for which the correlation coefficients are the best;
   - effect very frequently documented in the literature;
   - effect for which evaluation can be objective.

2. In the establishment of the dose-response relationship, only controlled studies were used. Studies performed in the workplace were used only as support since under these conditions, the exposure dose cannot be precisely estimated and the effects can often be attributable to products other than formaldehyde.

3. The selected studies cover a large area of the range of concentration susceptible to be present in the workplace (between 0 and 4 ppm) (14). The available studies also show various exposure durations. The durations vary between 90 seconds and three hours (13, 14, 58), which represents all of the possible situations that can be encountered in the workplace (continuous exposure, peak concentration for a relatively short duration, etc.). These studies made it possible to observe that there was no significant difference in the percentage of individuals experiencing irritations according to the duration of exposure to a given concentration. Therefore, the dose-response relationship was established according to the exposure concentration alone. The fact that the response does not vary depending on the duration of exposure is explained by the very fast metabolic rate of formaldehyde (approximately five minutes) (11). Thereby, the effects are reversible, stopping as soon as the exposure is stopped (13, 15, 19).

4. The dose-response relationship was also established from gathering all of the raw data from the various controlled studies that were considered in order to give equal weight to each individual and not to each study, where the number of subjects varied.

Moreover, on the basis of raw data, it was possible to take into account the degree of severity of the effects when establishing the relationship.

5. When establishing the dose-response relationship, with regard to eyes, nose and throat irritations, the controlled studies performed on asthmatic subjects were considered in the same manner as those performed on healthy subjects (see Tables 2 and 4). In fact, various authors of the controlled studies observed (see Table 1) that the asthmatic subjects did not seem to be more sensitive to irritations than the non-asthmatic subjects for concentrations of up to 3 ppm (8, 13, 58).

However, the approach used to establish the dose-response relationship had certain limitations:

1. The controlled studies had various degrees of confidence. The studies with low degree of confidence were not selected, but the studies with a moderately to high degree of confidence were considered in the same way.

2. The selected studies were analyzed to discern the irritating effects by degree of severity. The definition of a "moderate" effect was considered to be the same from one study to another, while it is impossible to be sure that the authors considered the same degree of severity. This is also true for the definition "mild" or "severe". Nevertheless, in several studies the qualifications of mild, moderate or severe were defined according to the degree of tolerance of the effects felt by the subjects of the study. The subjects, themselves, indicated subjectively if the effect experienced was tolerable or not (12, 14, 57). It is difficult to imagine that the experimenter would classify a serious and intolerable effect as being mild or moderate.

3. The authors do not always determine a degree of severity of the effect measured. In certain studies, the response percentage is comprised of all the individuals who experience an effect (eye irritation, for example), whatever its severity. In other studies, the authors only consider as a response those with a degree of severity higher than mild or moderate (8). When the information contained in these studies did not permit the classification based on the degree of severity, the classification was made based on a distribution similar to the one observed in other studies for which the classification was more precise. This distribution could possibly have a bias, but it is impossible to say in what direction. It is difficult to do better with the available data.

4. In the controlled studies selected to determine the dose-response relationship, the subjects were exposed for a maximum duration of three hours. Even if the effects of formaldehyde exposure do not seem to be cumulative with the duration of exposure due to the fast metabolism of formaldehyde, it is impossible to assert with certainty that the conditions of exposure in the workplace, eight hours per day, five days per week, for numerous years, would not lead to other effects, or to stronger effects (more severe, earlier, more sensitivity, etc.).

6.1.1.2 Characteristics of the studies used

It also seems to be important to mention certain aspects of the studies used to establish the dose-response relationship:

1. Controlled studies are often performed on a small number of subjects (in general, between 10 and 30) (10, 13, 60). This gives them limited power and does not make it possible to contend that if the number of subjects were much higher, the response percentages would remain the same.

2. In a large number of studies, very often the populations studied consisted of individuals who were more susceptible than the average. The subjects considered could be asthmatic, hypersensitive or have already experienced respiratory, allergic or irritating problems, or have complained of the effects of formaldehyde (8, 57-59, 80). This implies that the response percentages obtained for various concentrations could be overestimated with regard to the same response percentages in the general population.

3. There exists a problem of terminology in terms of classification of the irritating effects. According to the authors of the studies, the symptoms taken into consideration for attributing irritating effects are not always the same: for nose irritation, some consider nasal drip; others, tingling, itching, or even sneezing (14, 19).

4. Even when the studies are well performed, there is still a great intra- and inter-individual variability, so that there will always be a variation and a certain distribution of the results. Nevertheless, there does not seem to be a difference in the response percentage based on the sex of the individuals: men and women tend to respond the same way to formaldehyde exposure; also, age does not seem to vary the responses (3, 56).

5. However, numerous other factors exist that could produce effects similar to that of formaldehyde (cause eye, nose or throat irritation), or influence its effect (increase or reduce it) and explain this way, in part, the variations observed in the studies. These factors are (3, 81):

   - the exposure conditions (temperature, degree of humidity);
   - health condition of the subjects;
   - the number of hours of sleep the day before;
   - smoking habits of the subjects;
   - the presence of other chemical substances and dust;
   - the psychological factor of the perception of odor.

In buildings, the factor most often associated with symptoms of irritation of the nose and throat is undoubtedly a low level of humidity in the air.

1. Of all these factors, smoking surely deserves the most attention. In fact, a study made the comparison between exposure to cigarette smoke and formaldehyde (14). In addition to large quantities of formaldehyde, cigarette smoke contains numerous other irritating substances. Subjects exposed to the same quantities of formaldehyde but in two different forms – formaldehyde alone or present in cigarette smoke – experienced a more acute and intense eye irritation in the second case. At equal formaldehyde concentrations, cigarette smoke seems to be much more irritating than formaldehyde alone.

2. It is also important to mention that, because of inter-individual variations and the presence of numerous other factors, there are always subjects who are more sensitive. They will exhibit symptoms of irritation even at very low or almost non-existent concentrations. These effects represent the background noise value and they are not attributable to formaldehyde exposure. In several studies, the background noise value or the frequency of irritation in control groups was sometimes high, ranging from 5 to 15% in some studies (10, 57).

6.1.1.3 Generalization of the results of this analysis to workers in Quebec

The health risk to workers, attributable to formaldehyde exposure as calculated from the dose-response relationship data under controlled conditions, could be different from the actual risk for the following reasons:

1. Workers exposed to formaldehyde will have a tendency to protect themselves or to avoid exposure as soon as they perceive the odor. The threshold for perception of odor is very low, between 0.04 ppm and 1 ppm according to different authors (3, 7, 10, 13), and generally less than concentrations producing effects. This implies that workers could be less exposed than reflected in the exposure matrices data, particularly for ceiling values. In addition, it could be thought that an individual who senses a disagreeable effect that seems to be attributable to formaldehyde will tend to protect himself/herself or to spend a shorter time in the environment where the effect was felt.

2. In the studies used to establish the dose-response relationship, the concentrations were stable. In the workplace, however, formaldehyde concentrations fluctuate over time.

3. In controlled studies, subjects were exposed to formaldehyde in the form of vapor, although in industry, formaldehyde can be adsorbed at particle surface (wood dust). It was shown that the bioavailability of formaldehyde adsorbed at the surface of wood dust is only of about 3% (82). Pulmonary effects are not excluded, but they could be due more to wood dust than to formaldehyde.

4. As previously mentioned, several of the studies that were used to determine the dose-response relationship mostly involved subjects more sensitive than the average (8, 57, 58).

5. The working Quebec population includes a certain proportion of smokers. Several studies showed that smokers were less sensitive to formaldehyde, since

they are already exposed to irritating substances including formaldehyde and seem to demonstrate greater tolerance to irritants (14).

However, the present study concerned only formaldehyde exposure and its impact on health, while in the workplace, workers are rarely exposed to only one substance. It is possible that the presence of other irritating substances or wood dust exacerbates the irritating effect of formaldehyde and it increases the health risk for workers.

Nevertheless, it must be noted that complaints due to formaldehyde exposure reported to the CSST (Quebec Commission of Health and Occupational Safety) are rather rare. As for cases of protective reassignment, 11 cases were reported in four years among six CAEQ (Quebec Economic Activities Classification) codes, four business sectors and nine different occupations (83). No cases of occupational illness that were attributable to formaldehyde were reported in the same period.

6.1.2 Application of the dose-response relationship to workers in Quebec: mean values or ceiling values?

For the assessment of the impact of lowering the permissible exposure value, the dose-response relationship developed from literature data was applied to the exposure matrices of various industrial sectors in Quebec. (Refer to the global report and the sector Appendices of the final report for more details.) In reality, the risk for these workers is closer to that calculated from ceiling values than that calculated from average values because, as it was seen in control studies, humans respond to peak concentration after a relatively short duration. Of course, since the average value for several hours of exposure during a day integrates and smoothes the overall variations in the concentrations, the average value will be lower than the peaks that occur during this period.

Nevertheless, if one refers to the exposure data of the IRSST (The Robert-Suavé Workplace Health and Safety Research Institute in Quebec), the probability of frequent exposure to the ceiling values indicated in the matrices is low. The duration of the ceiling values in these matrices is about one minute each. In other words, a worker exposed to an average value for eight hours that was low, cannot have been exposed to ceiling values of a relatively high frequency and intensity. Otherwise, the average would be higher. At work, workers are exposed to formaldehyde concentrations that vary in time and space. Their exposure can therefore be theoretically represented by a distribution of ceiling value concentrations around an average value. (It is probably geometric for this type of exposure.) The result of this distribution is that the frequency of exposure to extreme values will be much lower than that at concentrations close to the average. These extreme values are equivalent to the ceiling values that constitute the ceiling exposure matrices established by the IRSST, whereas the 8-h time-weighted average exposure matrices represent the averages of these distributions.

6.1.3 Comparison to the evaluation performed by ACGIH

ACGIH also evaluated the health impact of formaldehyde exposure (49). The majority of the studies selected and analyzed for this evaluation were the same as the ones we have selected. The conclusions of these studies are therefore the same between the ACGIH analysis and this analysis. However, ACGIH went one step further than scientific evaluation. They proposed a recommendation of an acceptable ceiling limit of 0.3 ppm based on their own interpretation of the data. This recommendation is based on the desire to avoid a maximum of irritations in workers. This includes even the mildest irritation, given that some studies showed that the most sensitive people complained of irritation at concentrations as low as 0.3 ppm, without taking into account the degree of severity of effects (only the presence or absence of effect is taken into account, without giving more weight to more severe effects), or the population response at background level (in controlled studies, an equal or a higher incidence was observed at 0 ppm than at 0.3 ppm.). In addition, the quality difference between the controlled studies and the studies involving workers was not taken into account in the process of risk evaluation. The ACGIH therefore recommends a ceiling value of 0.3 ppm and specifies “concentrations should be reduced to the lowest levels detectable by the measuring equipment.” It must also be mentioned that the ACGIH is not a regulatory organization.

6.1.4 Comparison to the evaluation performed by Paustenbach *et al.*

A study by Paustenbach *et al*. (79) also attempted to establish the dose-response relationship between formaldehyde exposure and the percentage of subjects with eye irritation. This relationship was determined by the following equation:

$$\% \text{ response} = 19.6 + (17.4 \times \text{concentration of formaldehyde in ppm})$$

Nevertheless, in this study, the dose-response relationship was determined based on the mean percentage of irritating effects reported in the various studies, independent of the number of subjects (instead of giving equal weight to each subject as in this work). In addition, not only were controlled studies considered in the determination of the dose-response relationship, but studies showing a lower confidence level were also considered, that is, studies performed in the workplace. The background noise in the general population was not subtracted, and the irritation classification was not based on the degree of severity of the effect (mild, moderate, or severe irritation). In spite of a methodology, which was different from the one used in this study, it was concluded that a ceiling value of 1 ppm for 15 minutes was appropriate to prevent moderate, although transitory, eye irritation. The authors also stated that at such concentrations, formaldehyde should not cause eye irritation in at least 75% of workers and possibly up to 95%.

6.2 Effects due to subacute to subchronic exposure

A few studies, in individuals with occupational exposure to formaldehyde, conducted either in a controlled environment or not, reported effects on the pulmonary function, while others did not show an association, for formaldehyde concentrations up to 2 or 3 ppm. In this type of studies, the presence of uncontrolled confounding factors—other substances that could provoke the same symptoms—did not definitely incriminate formaldehyde as the causal agent in this effect (9, 17, 80). Moreover, exposure in the workplace was very difficult to quantify, because the concentrations were not measured at the workstations (6, 9, 18, 19, 84). The effects, when present, disappeared after cessation of exposure (17, 19). In addition, the specificity of this type of test is too low to avoid a significant number of false positives, producing a weak predictive value, particularly when the prevalence is low (85).

Controlled studies involving healthy and asthmatic subjects without documented occupational exposure showed no significant change in the pulmonary function, bronchial reactivity, or bronchoconstriction following one or more exposures to formaldehyde concentrations ≤2 ppm (12, 57-60). The response of asthmatics was similar to that of healthy individuals. Based on the latter controlled studies, the impact on workers' health of lowering the standard from 2 ppm to 1, 0.75, or 0.3 ppm ceiling values appeared to be negligible as far as the effects on respiratory function and the appearance of asthma attacks are concerned. Exposure in the experimental studies was nevertheless of short duration contrary to the case of workers who can be exposed every day for several years at those levels.

6.3 Effects due to chronic exposure

6.3.1 Epidemiological studies

Epidemiological studies are one of the only tools available to evaluate the effects related to chronic exposure in humans. They are therefore useful and necessary for verifying if a causal relationship exists between long-term formaldehyde exposure and excess cancer risk in the exposed population. However, all these studies, whether cohort, case-control, or meta-analysis, have limitations and biases of which we have to be conscious.

6.3.1.1 Limitations of epidemiological studies

The first limitation resides in the difficulty in classifying the exposure especially for *a posteriori* studies (case-control studies). This is also the case for an ill person who tends to remember more exposures than healthy people do. In addition, the interviews were conducted with full knowledge of the status (case or control), which means that bias is therefore possible in classification. Note also that no direct formaldehyde measurements were taken for the case-control studies (21, 31, 64). For cohort studies, measurements were taken sporadically and sometimes several years after the workers' exposure and this limits the confidence in the exposure data (24, 25, 33, 38, 74).

Control of confounding and modifying factors also plays an important role in the quality of epidemiological studies. In many studies—cohort, case-control, and meta-analysis—several potential confounding factors were evaluated and included in the statistical model if necessary (26, 29, 72). Nevertheless, no study controlled all possible confounding factors. For all studies, therefore, it cannot be excluded that a factor other than formaldehyde could contribute to the increase in the incidence of cancer. If such a factor is not uniformly distributed between the exposed and non-exposed groups, a bias will be introduced. Fine sawdust, alcohol, food, social class, and smoking are part of the potential cancer risk factors in cancer studies that were not always controlled (30, 33, 38, 62, 65, 71). Other chemical substances and the EBV virus could also present a potential risk.

In many studies, the incidence of cancers of the upper respiratory tract is evaluated globally without distinguishing different types of cancers of a same anatomical region. This evaluation did not find significant risk. A separate and more systematic evaluation of various types of cancer (squamous cell carcinoma and adenocarcinoma for the sinuses and nasal passages, the nasopharynx and oropharynx for the pharynx, etc.) could have confirmed the tendencies observed in some studies (21-23).

Several studies evaluated cumulative exposure, which does not seem very useful (21, 28, 32, 67, 68). The severity of damage seemed to be related to the air concentration of formaldehyde reached rather than to cumulative exposure (86). In fact, it is not obvious that the risk of exposure to 2 ppm for two years is the same as the one for an exposure to 0.2 ppm for 20 years.

Most of the selected studies included a very low number of cases, which results in a lack of power. Some results were statistically significant, and others were not, and confidence intervals were rather wide (25, 29, 34, 65, 73), which limits the precision and the conclusions that can be drawn. Nevertheless, in theory, meta-analyses have a major advantage as compared to cohort studies and case-control studies. They generally have an interesting power (26, 27, 35). However, since meta-analyses are constituted of cohort and case-control studies, their limitations are the same as those of the studies they use. Furthermore, several questions need to be addressed that could introduce a bias, for example: are the methods used in studies comparable, or should studies be limited to those which meet additional quality-control criteria? Thus, a wrong classification of exposure is possible, the assessment of exposure differs among studies and, if the classification is biased in most studies, this will be the case for the meta-analysis as well. The types of cancer observed were not necessarily the same in all various studies. The results of one large study could have a great influence on the results of the meta-analysis given its relative weight in the meta-analysis. It is important to keep in mind that all meta-analyses published include essentially the same studies and that only a few studies were different. In fact, they were often limited to containing studies whose comparisons were not always obvious.

The types of cancer evaluated in these epidemiological studies are rather rare in the general population. It is therefore understandable that few cases were observed (38, 42, 71-73). This does not exclude the fact that there could have been more cases if the groups had been larger. Even in the case-control studies, the rarity of these types of cancer in the general population limited the number of cases available for constituting these studies.

In several studies, the PMR, PCMR, or the SPIR were used for risk analysis (25, 42, 71, 72). With these analysis methods, the relative frequency of other causes of death could modify the proportional mortality ratio (PMR) of the cancer of interest. If the number of deaths in the study group were low because of other causes of death, the PMR for the cause of interest could be artificially high.

A healthy worker effect is possible, given that the comparison was made with the general population in most of the studies. Workers are normally healthier than the general population. The healthy worker effect was controlled in two studies (25, 73). One study took the comparison group from the Danish supplemental pension fund constituted only of workers. Another study used non-exposed workers as a comparison group in addition to the general population.

In short, analysis of the selected epidemiological studies demonstrates that some studies showed an association between formaldehyde exposure and cancer, while other studies did not show such a relationship. Nevertheless, all these epidemiological studies have methodological limitations that reduce the confidence level of the results. These limitations are mainly lack of power, the presence of confounding factors, the fact that an effect is observed in the least exposed groups and but no effect in the most exposed groups, the lack of measurement of exposure level in numerous cases, or sporadic measurements. Consequently, there is limited proof of the carcinogenic potential of formaldehyde in epidemiological studies but it is not possible, based on epidemiological studies, to establish a dose-response relationship between formaldehyde exposure and the onset of cancer within the concentration limits of the permissible exposure value.

Likewise, most reference and regulatory organizations arrive at similar conclusions with respect to the analysis of epidemiological studies. Nevertheless, a number of these bodies classify formaldehyde as a possibly carcinogenic substance (see introduction section) based on the results of animal data. Indeed, several animal studies showed that formaldehyde caused nose cancer in rats at 5.6 ppm and higher (76). Based on these animal data supported by the carcinogenic mechanisms of action, only two organizations, the U.S. EPA and the CIIT, have proposed a dose-response relationship that quantifies the carcinogenic risk.

6.3.2 The U.S. EPA approach and its limitations

Initially, the EPA proposed an initial attributable cancer risk value (ERC) based solely on animal data and calculated after applying the multistage model linearization procedure (51). But, the inconsistency of the results provided by this model when confronted with different data sets, the analysis of the incidence of nose cancer in the general population, and the highly non-linear animal data related to tumors, indicate that this procedure was not appropriate for this situation (87) and that a reevaluation was necessary. In addition, the dose scales of the first evaluation were represented by external exposure doses, while the risk estimates based on measurements of effects such as the number of DNA-formaldehyde/formaldehyde-protein bonds were much lower. These aspects were taken into consideration by the U.S. EPA, which consequently reviewed its position on risk evaluation in 1991 (52) and proposed an adjusted value of the excess unit risk coefficient, which still remains very conservative.

6.3.3 The CIIT study (1999): advantages and limitations

In order to predict the risk of cancer as a consequence of formaldehyde exposure, the CIIT proposed a two-stage carcinogenesis model based principally on animal data (75). The strength of this model comes from the fact that it takes into account the different carcinogenic mechanisms of action—the direct mutagenic effect (by binding to DNA) as well as the cytotoxic potential—and that it was validated with the epidemiological data of studies where an excess of cancer was observed. The CIIT also proposed several prediction values of cancer risk according to the selected scenario—occupational or non-occupational exposure, and smoking or non-smoking subject. Taking into account these different scenarios makes it possible to get as close as possible to reality.

6.3.4 Comparison of the U.S. EPA and CIIT estimates

If we compare the excess risks found by the U.S. EPA in the 1991 evaluation to those found by the CIIT, regarding an environmental exposure of 0.1 ppm (continuous exposure for 80 years, 24 hours a day), the EPA model gives an excess risk between 3.3×10^{-5} and 2.8×10^{-4}, while the CIIT estimated the excess risk between 2.7×10^{-8} and 6.7×10^{-7}. The ratio of the two estimates of excess risk is between 500 and 1000 depending on the scenario, the U.S. EPA being much more conservative than the CIIT. It is obvious that the U.S. EPA model does not represent reality, because the number of cases of cancer, estimated with the their approach would be 500 to 1000 times higher than observed in the epidemiological studies.

7 CONCLUSION

7.1 Effects due to acute exposure

The dose-response relationship between formaldehyde exposure and the appearance of eye, nose, and throat irritation was established based on data from controlled studies. Our analysis indicates that, for concentrations less than 0.75 ppm, the frequency of irritation in workers exposed to formaldehyde was about the same as the one observed in individuals without occupational exposure. This means that appearance of irritation at such concentrations can hardly be associated with occupational exposure to formaldehyde. For concentrations between 0.75 and 3 ppm, the estimated proportion of workers who may experience moderate irritating effects to the eyes, nose, and throat, attributed to formaldehyde is between 1.6 and 14.9%. It was estimated that at most 2% of workers could have severe eye irritation. In the case of occupational exposure, we cannot exclude the fact that factors other than formaldehyde, such as wood dust, could be the cause of irritating effects or they could increase the probability that these effects would occur through synergy with formaldehyde.

7.2 Effects due to subacute to subchronic exposure

The relationship between formaldehyde exposure and the occurrence of subacute and subchronic effects was established based on *i)* controlled studies (inhalation chamber) in individuals with and without known occupational exposure and *ii)* field studies.

The majority of studies carried out in a controlled environment involving healthy and asthmatic subjects, without documented occupational exposure, did not observe any significant change in the pulmonary function, bronchial reactivity, or bronchoconstriction for exposure concentrations of up to 2 or 3 ppm. Among the studies in which workers were exposed to 1 to 2 ppm of formaldehyde in inhalation chambers, a few rare cases of asthmatic reactions were reported but only in individuals with known respiratory problems. In all cases, discontinuation of the exposure led to resolution of the symptoms.

In the workplace, some studies reported a decrease in some parameters of the respiratory function in a few workers exposed to formaldehyde concentrations of up to 2.0 ppm. In this type of study however, it is not possible to dissociate the contribution of formaldehyde from that of other substances. In addition, the sensitivity and specificity of these types of tests are too low to avoid a significant number of false positives, resulting in a weak predictive value when the prevalence is low.

7.3 Effects due to chronic exposure

Our analysis aimed to verify if the overall epidemiological studies allows to establish a causality link between formaldehyde and the cancers observed in some studies. We came to the following conclusion: because of the inconsistencies among the results of studies regarding the association and strength of association, frequent methodological limitations such as lack of power and a limited determination of actual exposure, the inability of cohort studies to observe an increased risk because the studied types of cancer are rare, and the lack of a dose-response relationship that increases with increasing doses, the evidence for a causal association is very limited, although it cannot be entirely excluded. In animals, the proof of a causal relationship appeared sufficient to us, but the increase in cancer was observed only at high concentrations. The cellular alterations in the tissues of the respiratory tract make this relationship plausible. It must be remembered, however, that the concentrations at which an excess of cancer was observed in animals also induce severe irritation. These factors can contribute to a significant increase in cancer risk through an epigenetic or promoter mechanism. These observations suggest that at concentrations at which irritation is low or non-existent, the cancer risk, if any, increases more slowly with the increase in dose than when irritation is severe and chronically present. At the concentrations at which cancer was observed in animals (5.6 ppm and higher), no worker could remain in his work environment, because irritation to the respiratory tract and eyes would be completely intolerable.

For these reasons, as far as the estimations of excess risk are concerned, based on high-to-low dose mathematical extrapolation models, the CIIT model appears more appropriate than the U.S. EPA model in estimating the workers' risk. This is especially true since the estimates of this model for low doses approach the levels of excess risk observed in the epidemiological studies where a positive statistical association was observed.

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9 APPENDICES

Appendix 1: Effects of formaldehyde on human and animal health, NOAEL and LOAEL (extract from the preliminary report by Yvette Bonvalot)

Appendix 2: The relationship between exposure to formaldehyde and cancer of the upper respiratory tract in humans (extract from the work directed by Sandra Fradet)

Appendix 1: Effects of formaldehyde on human and animal health, NOAEL and LOAEL (extract from the preliminary report by Yvette Bonvalot)

Effects of formaldehyde on health following respiratory exposure at levels equal or inferior to those of the current permissible exposure value in Quebec

Several studies, both animal and human, seem to show the occurrence of effects following short-term exposure to formaldehyde through inhalation. At the levels with which we are concerned, these effects seem to be largely on the respiratory tract.

Respiratory effects due to acute exposure in animals

Eight studies (6 in rats, 1 in mice and 1 in guinea pigs) involved this type of effect at levels near or inferior to that with which we are concerned in this case: i.e., 2 ppm.

Chang *et al.* (1981) studied the impact on various respiratory parameters of a single or repeated exposure to formaldehyde in male F-344 rats and male B6C3F1 mice. Three groups of rats and mice were pretreated, 6 hours a day for 4 days, at levels of 2, 6 and 15 ppm. From 18 to 24 hours after the pretreatment, these groups of animals, as well as non-pretreated groups, were exposed for 10 minutes to levels varying between 0.4 and 56 ppm. The respiratory rates of the pretreated rats and mice were significantly diminished compared with those observed in the non-pretreated animals (17% in rats regardless of the pretreatment level, and from 10% to 30% in mice). Each group exposed to a given level was comprised of 3 to 4 animals.

Monteriro-Riviere and Popp (1986) exposed male F-344 rats, aged 7 to 9 weeks, to formaldehyde levels of 0.5, 2 and 6 ppm, for 6 hours a day over a period 1, 2 or 4 days. The animals were euthanatized 18 hours after the end of their exposure. Only very slight changes could be observed on the ciliated cells of the respiratory tract at levels of 0.5 and 2 ppm, but these changes could also be observed in the controls. On the other hand, exposure to a level of 6 ppm for 1 day resulted in the presence of autophagous vacuoles and neutrophils, and also in a loss of microvilli in the ciliated cells, and hypertrophy of the glandular cells and the ciliated cells of the nasal passages. The exposed groups, as well as the control group, were comprised of 5 rats, but only 3 rats from each exposed group were examined in detail.

Monticello *et al.* (1991) exposed six groups of 36 male F-344 rats, initially aged between 6 and 7 weeks, to formaldehyde levels of 0, 0.7, 2, 6, 10 and 15 ppm. They were exposed for 6 hours a day during 1, 4 or 9 days to study the acute effects and for 6 weeks, 5 days a week, to study the subchronic effects. Within 18 hours after the end of their exposure, the animals received an intra-peritoneal injection of tritiated thymidine (^{3}H-thymidine), then were euthanatized 2 hours afterwards. No evidence of a lesion due to exposure to formaldehyde was demonstrated in the animals exposed to 0.7 to 2 ppm. At 6 ppm, lesions were localized and consisted in necroses of the nasal epithelial cells, infiltration of the neutrophils, epithelial hyperplasia, squamous metaplasia and an increase in cell proliferation. The groups exposed to 10 and 15 ppm showed lesions, the gravity and extent of which became more significant the longer they were exposed. A statistically significant increase in cell proliferation was

observed starting at 6 ppm. According to the authors, the responses observed in rats at 6 ppm are similar to those reported for rhesus monkeys, but show a different distribution (localization).

Morgan *et al.* (1986a) exposed four groups of 3 male F-344 rats to a formaldehyde level of 15 ppm for 10, 20, 45 or 90 minutes, as well as a group of 6 male F-344 rats to this same concentration for 6 hours. Two other groups of 3 rats were also exposed to 2 ppm of formaldehyde for 90 minutes and 6 hours, while nine other rats were exposed to the ambient air in the inhalation system for 6 hours and served as controls in regard to ciliary activity, the distribution and the rate of mucus. All these animals were examined as quickly as possible after their exposure in order to assess the nasal mucociliary activity. Other groups of 3 rats exposed to 15 ppm for 90 minutes and 6 hours were examined 1 hour after having been exposed to the ambient air in order to evaluate the recovery potential of the nasal mucociliary function. Exposure of the rats to 2 ppm of formaldehyde for 90 minutes and 6 hours did not alter the nasal mucociliary activity. On the other hand, at 15 ppm, the extent of the effects on the mucociliary function showed itself to be dependent on the duration of exposure, with larger mucostatic and ciliastatic surfaces after 6 hours of exposure. One hour of exposure to the ambient air, following the rats' exposure to 15 ppm of formaldehyde, resulted in a very clear-cut recovery of the mucociliary function. It resulted in almost complete recovery for the rats exposed for 90 minutes.

Morgan *et al.* (1986b) also studied the effects of an acute exposure to formaldehyde for longer durations on the nasal mucociliary tract of male F-344 rats. For that, they exposed groups of 3 rats to levels of 0, 0.5, 2, 6 and 15 ppm, 6 hours a day for 1, 2, 4, 9 or 14 days (5 days per week). Inhibition of the nasal mucociliary function proved to be clearly less severe at 6 ppm than at 15 ppm, minimal at 2 ppm and undetectable at 0.5 ppm. Exposure to 15 ppm of formaldehyde induced inhibition of the nasal mucociliary function in specific regions of the nose, with greater mucostasis than ciliastasis. Nasal drip, mucostasis, ciliastasis, inflammation, proliferation of epithelial cells, infiltration of neutrophils, coagulation of mucus and exfoliation of ciliated and non-ciliated cells were a part of the poorly significant histopathological effects observed at 2 ppm, while nasal ulcerations (significant effect) could be observed at 6 ppm.

Swiecichowski *et al.* (1993) studied the potential, in Hartley guinea pigs, for induction of hyperreactivity in the airways following exposure to formaldehyde. The pulmonary resistance of each guinea pig was measured beforehand [and] 5, 7.5, 10, 15, 20, 25, 30 and 60 minutes after exposure, while the reactivity of the airways was measured beforehand [and] 1, 2, 6 and 24 hours after a 2-hour exposure, and 1, 2, 3 and 24 hours after an 8-hour exposure. Using these measurement sequences, groups of 5 to 7 guinea pigs were exposed to 0.86, 3.4, 9.4 or 31.1 ppm for 2 hours, and to 0.11, 0.31, 0.59 or 1.05 ppm for 8 hours. The controls were exposed to the ambient air for 2 or 8 hours. Exposure to formaldehyde caused bronchoconstriction as well as hyperreactivity at the weakest concentrations when the duration of exposure was 8 hours. Exposure to levels equal to or greater than 0.3 ppm of formaldehyde for 8 hours proved to be sufficient to induce a significant increase in the reactivity of the airways (an increase in the respiratory resistance), while similar effects occurred after 2 hours of exposure only at levels greater than 9 ppm. According to the authors, the results of this study suggest that the duration of exposure is an important factor in the induction of muscular hyperreactivity in the respiratory tract, and that, when

prolonged, exposure to weak levels can generate abnormal physiological responses, not detected at the time of acute exposure (at higher levels over shorter periods).

As for Woutersen *et al.* (1987), they studied the effects of exposure, in male and female albino Wistar rats, on cell proliferation at levels of 1, 10 and 20 ppm of formaldehyde for 6 hours a day during 3 days. Four groups of 2 animals were thus exposed (1 control group and 3 exposed groups). After three days of exposure, the renewal of cells in the nasal passages was higher for the groups exposed to 10 and 20 ppm. This regeneration took place in the areas where metaplasia and squamous hyperplasia were visible.

Other effects due to acute exposure in animals

No other systemic effect, whether cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine or global, such as loss of weight, consecutive to a short-term exposure (14 days and fewer) was shown in laboratory animals at the levels that interest us.

Respiratory effects due to acute exposure in humans

Gorski *et al.* (1992) researched the pulmonary effects of exposure, through inhalation, to 0.5 mg/m^3 (0.41 ppm) of formaldehyde for 2 hours in 13 patients who displayed contact dermatitis after occupational exposure to formaldehyde and in 5 healthy volunteers. No modification in the various spirometric parameters was observed (vital capacity, forced expiratory volume and maximum expiratory volume).

Green *et al.* (1987) studied the pulmonary effects of formaldehyde in 22 healthy subjects and in 16 asthmatics. These 38 non-smokers were randomly exposed for 1 hour to the ambient air or to 3 ppm of formaldehyde over two distinct days; thus, the subjects were their own controls. During the hour of exposure, the healthy individuals performed intermittent but intense physical exercise, while the asthmatics performed intermittent and moderate exercise. The two groups of individuals displayed similar and significant responses in the olfactory perception as well as irritation of the nose, throat and eyes during exposure. Slight decreases both in the forced expiratory volume (FEV) and in forced vital capacity (FVC) were observed only in the healthy subjects, but not in the asthmatics, who performed, however, a lower level of exercise. Finally, five of the 38 subjects studied showed decreases in FEV_1 (forced expiratory volume for 1 second) of more than 10%. The authors then concluded that exposure for 1 hour to 3 ppm of formaldehyde caused symptoms of irritation both in healthy subjects and in asthmatics, slight decreases in pulmonary function in normal subjects performing intense exercise, and clinically significant responses such as a decrease in $FEV_1 \geq$ 10% in 13% of the individuals studied.

Harving *et al.* (1990) studied, in 15 asthmatics (8 women and 7 men aged between 15 and 36 years old), whether exposure to formaldehyde at levels similar to those found inside the premises could produce adverse effects in the lower respiratory tract. The participants were randomly assigned to one of the 3 groups of 5 individuals. Each of these three groups followed the same sequence of randomly defined exposure, and was exposed for 90 minutes on the same day of the week for 3 weeks to 0, 0.12 mg/m^3 (or ≈ 0.1 ppm) and 0.85 mg/m^3 (or ≈ 0.7 ppm) of formaldehyde. No change was observed regardless of the concentration, tested, either for pulmonary function, or for symptoms of asthma or for bronchial reactivity.

Kulle *et al.* (1987) analyzed the effects of exposure to formaldehyde on the pulmonary function in 19 healthy non-smoking subjects. The subjects, who were their own controls, experienced 5 periods of exposure of 3 hours each. An initial group of 10 subjects was randomly exposed to concentrations of 0, 0.5, 1 and 2 ppm at rest, and to 2 ppm while performing moderate exercise. The second group of 9 subjects was randomly exposed to concentrations of 0, 1, 2 and 3 ppm at rest, and to 2 ppm while performing moderate exercise. One week of "rest" separated each period of exposure. No alteration in the respiratory function was demonstrated either at rest or during moderate exercise. On the other hand, a significant linear "dose-response" relationship could be observed for the olfactory perception and the incidence of eye irritation in the 9 subjects exposed between 0 and 3 ppm. Exercise resulted in no increase in the olfactory perception or eye irritation, but significantly increased irritation of the nose and throat. The authors concluded that exposure to levels of formaldehyde ranging between 0.5 and 3 ppm did not diminish the respiratory function of healthy adults but caused symptoms of irritation in the upper respiratory tract.

Nordman *et al.* (1985) were interested in the prevalence of cases of asthma induced by exposure to formaldehyde. A total of 230 individuals (men and women), who had been exposed to formaldehyde and suffered from symptoms of asthma were included in the study. On the basis of the medical and occupational history of the individuals, as well as the results of certain tests, 12 cases of asthma were identified as directly attributable to a specific sensitization to formaldehyde. When exposed to 2 ppm of formaldehyde for 30 minutes, 8 subjects had an immediate bronchial reaction accompanied by a decrease in expiratory peaks ranging between 19% and 49%, while 4 subjects had a delayed bronchial reaction accompanied by a decrease in expiratory peaks ranging between 21% and 47%. Let us note that the authors concluded that the cases of asthma induced by formaldehyde were under-declared, that suppression of exposure had a favorable effect on the reduction of symptoms, but that levels as weak as those observed in the houses could maintain the symptoms observed in individuals already sensitized. However, this is the only study that discusses this potential effect of formaldehyde, without demonstrating the dose-response relationship and with certain methodological limitations that caution in the interpretation of its conclusions.

Pazdrak *et al.* (1993) conducted a study in non-smoking volunteers, the goal of which was to characterize the nature of the nasal responses induced by exposure to formaldehyde, which consist of symptoms of rhinitis and changes in nasal flushings. An initial group of 9 subjects (6 men and 3 women) exposed occupationally to gaseous formaldehyde or to solutions of formalin displayed cutaneous hypersensitivity to formaldehyde, while the second control group of 11 healthy male subjects had no allergy history. The subjects of each of these two groups were all exposed for 2 hours either to a placebo or to 0.41 ppm of formaldehyde, and nasal flushing was performed before exposure, immediately after, then 4 hours and 8 hours after exposure. It follows from this study that the subjects exposed to 0.41 ppm of

formaldehyde displayed transitory symptoms of rhinitis (sneezing, congestion) and histological changes in the nasal flushings (increases in the eosinophilic and albumin levels, decreases in the number of epithelial cells in the samples of the nasal flushings). No difference in the nasal response was observed between the patients stricken with cutaneous hypersensitivity to formaldehyde and the patients not stricken with said cutaneous hypersensitivity.

Reed and Frigas (1985) attempted to demonstrate a relationship between exposure to formaldehyde and the development of symptoms of asthma in 13 individuals (11 women and 2 men) who had been exposed either at home or at work to levels of formaldehyde ranging between 0.1 and 1.2 ppm. These individuals reported symptoms of chest tightness, coughing and wheezing, which they attributed to their exposure to gaseous formaldehyde. Each of the 13 subjects was exposed to a placebo or to levels of 0.1, 1 and then 3 ppm of formaldehyde and were subject to spirometric tests before and immediately after exposure and then 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours and 24 hours after exposure. Only one patient displayed a significant decrease in FEV_1 (> 20%), but this decrease was similar to that observed with the placebo. For all the other individuals, no significant decreases in FEV_1 were observed. On the other hand, the incidence of symptoms such as irritation of the eyes, nose or throat as well as chest tightness proved more frequent after exposure to formaldehyde than to the placebo. The authors concluded that exposure to levels of 3 ppm of formaldehyde did not cause asthma attacks in these individuals.

Sauder *et al.* (1986), in turn, studied the pulmonary response to an exposure to 3 ppm of formaldehyde for 3 hours during intermittent exercise in nine healthy, non-smoking subjects of both sexes. Each subject was his or her own control and received pure air on day 1, and 3 ppm of formaldehyde for 3 hours on day 2. Various spirometric measurements were taken at t = 0, 30, 60, 90, 120, 150 and 180 minutes. The individuals exercised on a bicycle for 8 minutes, which ended 2 minutes before the taking of the spirometric measurements (except at t = 0). Exposure to formaldehyde for 30 minutes led to significant decreases in FEV_1 (2%; $p<0.05$) as well as in intermediate forced expiratory volume $FEF_{25\%-75\%}$ (7%; $p<0.01$). Nevertheless, these effects disappeared 60 and 180 minutes post-exposure. No change in the reactivity of the airways or the pulmonary function was observed 24 hours after exposure. The authors concluded that acute exposure to 3 ppm of formaldehyde was likely to induce small transitory decreases in pulmonary function as well as mild to moderate irritation of the eyes and upper airways.

Sauder *et al.* (1987) studied the pulmonary response after 3 hours of exposure to 3 ppm in 9 non-smoking asthmatic subjects (5 women and 4 men). Resuming the same protocol as in their preceding study (Sauder *et al.,* 1986), the subjects were exposed to pure air on day 1 and to 3 ppm of formaldehyde 7 days later. Various measurements and questionnaires were completed for each exposure. According to this study, inhalation of 3 ppm of formaldehyde for 3 hours does not affect the pulmonary function in a significant manner. On the other hand, a significant increase in reported symptoms could be observed during exposure to formaldehyde. These symptoms included irritation of the nose and throat (after 30 minutes of exposure), and irritation of the eyes after 60 and 180 minutes of exposure to formaldehyde. Per the authors, short exposure to 3 ppm of formaldehyde at rest should not cause bronchoconstriction in asthmatic subjects, but might induce irritation of the eyes and upper respiratory tract.

Schachter *et al.* (1986) assessed the effects of exposure to formaldehyde on the pulmonary function of fifteen healthy, non-smokers (9 men and 6 women) both at rest and performing moderate exercise for 10 minutes. These individuals were exposed randomly, in a double blind test, to 0 or 2 ppm of formaldehyde for 40 minutes in an experimental chamber with or without moderate exercise. Four periods distributed over 4 different days were thus tested according to a random sequence for each individual: at rest to 0 ppm and 2 ppm, and while performing moderate exercise at 0 and 2 ppm. Various spirometric measurements were taken before, during and after exposure (up to 8 hours and 24 hours afterwards using a questionnaire). No significant bronchoconstriction was noted in this group. The respiratory symptoms were generally confined to the upper airways and were mild to moderate in severity. The authors concluded that short exposure to 2 ppm of formaldehyde does not lead to acute or subacute changes in the pulmonary function in healthy individuals either at rest or performing moderate exercise. In fact, at 2 ppm, only a few symptoms of irritation of the upper airways were reported—symptoms qualified by the authors, moreover, as subjective.

Witek *et al.* (1986) studied the effects of exposure to formaldehyde on the pulmonary function of healthy individuals and asthmatics, at rest or exercising. A protocol similar to the one described in the preceding study was used (Schachter *et al.* 1986). Exposure to formaldehyde caused no significant change in the respiratory function either in the healthy subjects or in the asthmatic subjects. Nevertheless, just as before, an increase in symptoms of nose irritation or dry throat was noted. In 1987, these same authors repeated this study in 15 voluntary asthmatic subjects (Witek *et al.,* 1987). The conclusions proved similar to those obtained both by Schachter *et al.* (1986) and by Witek *et al.* (1986): *viz*., essentially symptoms of nose irritation or dry throat.

Hematological effects due to acute exposure in humans

In a study, of which the objective was the immunological response of asthmatics exposed to formaldehyde through insulation products (UFFI) and non-exposed asthmatics, no difference in the populations of white blood cells (lymphocytes, neutrophils, etc.) was observed between the two groups after exposure to 1 ppm for 3 hours (Pross *et al.,* 1987). The study included non-asthmatics (n=2) and asthmatics (n=4) who lived in "normal" houses, as well as 23 asthmatics exposed to urea-formaldehyde foam insulation (UFFI) products in their homes, and the blood analyses were conducted before and after exposure.

Immunological and lymphoreticular effects due to acute exposure in humans

Two studies were concerned with this type of effect following exposure through inhalation. The first of these two studies (Gorski *et al.,* 1992) demonstrated that exposure to 0.41 ppm for 2 hours caused an increase in the detection of granules present in the white blood cells of peripheral blood through a technique of chemiluminescence. The second did not permit observation of an effect for an exposure level of 1 ppm of formaldehyde for three hours (it was conducted among asthmatics exposed to formaldehyde through insulation products (UFFI or *urea-formaldehyde foam insulation)* and among asthmatics not exposed to these products (Pross *et al.,* 1987). This result seems, moreover, to conflict with the study of Pazdrak *et al.* (1993), which showed histologically visible effects in the nose at an exposure level of 0.41 ppm.

Respiratory effects due to subchronic exposure in animals

Appelman *et al.* (1988) examined the impact of exposure to formaldehyde on pre-existing nasal lesions in male Wistar rats exposed to 0, 0.1, 1 and 10 ppm of formaldehyde for 6 hours a day, 5 days a week during 13 or 52 weeks. Each of the 4 groups of rats was comprised of 40 animals, half of which (n=20) experienced nasal damage through electro-coagulation. After 13 weeks, in each of the 4 groups, 10 animals without nasal damage and 10 animals with nasal damage were euthanatized. The remaining rats continued the experience up to 52 weeks when they in turn were euthanatized. Histological examinations revealed rhinitis, hyperplasia and metaplasia of the respiratory epithelium of the rats exposed to the highest concentration of formaldehyde (10 ppm). The authors concluded that exposure to 1 ppm of formaldehyde did not affect the nasal epithelium in a visible manner and that exposure to 10 ppm did not affect the organs farther away. The damaged noses seemed to be more susceptible to a cytotoxic effect of formaldehyde. After 52 weeks, only the rats with the damaged noses showed squamous metaplasia at concentrations of 0.1 to 1 ppm of formaldehyde.

Casanova *et al.* (1994) were interested in the DNA-formaldehyde/formaldehyde-protein (or *DNA-protein cross-links*) links produced after a single exposure to radioactively labeled formaldehyde. The experiment involved 13 groups of 20 F-344 rats each (10 that were not pre-exposed and 10 pre-exposed at 0.7, 2, 6 or 15 ppm of formaldehyde for 11 weeks and 4 days, 5 days per week and 6 hours per day). On the 5^{th} day of the 12^{th} week, the pre-exposed rats and the rats that were not pre-exposed were exposed for 3 hours to a concentration equivalent to their pre-exposure with labeled formaldehyde. Exposure between 0.7 and 2 ppm did not lead to any histological difference in the mucous membrane between the pre-exposed rats and those not pre-exposed when compared to the control subjects. Exposures to 6, 10 and 15 ppm of formaldehyde caused histological lesions such as epithelial hypertrophy, hyperplasia and squamous metaplasia, with epithelium erosion and infiltration of neutrophils. Carbon-14 incorporation was significantly higher at levels of 6 and 15 ppm.

Maronpont *et al.* (1986) were interested in the effect of exposure to formaldehyde in B6C3F1 mice exposed, for 6 hours per day, 5 days per week for 13 weeks, to concentrations of 0, 2, 4, 10, 20 and 40 ppm of formaldehyde. Ten male mice and ten female mice made up each of the experimental groups. Severe effects, including death for the highest level, were observed at levels of exposure varying between 10 and 40 ppm. In female mice, no lesions were noted at levels below or equal to 4 ppm, whereas in the male mice, at 4 ppm and over, squamous metaplasia of the nasal cavity was observed in one mouse. Starting at 4 ppm in male mice and 10 ppm in female mice, significant effects were observed: squamous metaplasia, keratinization, purulent inflammation and serious discharge, as well as epithelial degeneration in nasal sections and dyspnea.

As we have previously seen, Monticello *et al.* (1991) exposed six groups of 36 male F-344 rats between 6 and 7 weeks of age to levels of 0, 0.7, 2, 6, 10 and 15 ppm for 6 hours a day, 5 days per week during 6 weeks, in order to study the subchronic effects. The results were presented in a more detailed manner in Section 2.1.1 of this document. We should recall that this study did not show any effect up to 2 ppm, and that the significant effects, such as necrosis of the nasal epithelial cells and an increase in the cellular proliferation, appeared at 6 ppm.

Rusch *et al.* (1983) studied the toxicity of formaldehyde in Cynomolgus monkeys by exposing them, for 26 weeks, 7 days per week, 22 hours per day, to concentrations of 0, 0.19, 0.98 and 2.95 ppm of formaldehyde. Each of the two control groups and three exposed groups were comprised of 6 male monkeys. The monkeys exposed to the highest concentrations (2.95 ppm) exhibited an increase in hoarseness, nasal congestion and discharge, and histopathological changes of the nasal epithelium: hyperplasia and squamous metaplasia, particularly during the last 13 weeks of the study. No signs of toxicity appeared at the lower levels.

In this same study, Rusch *et al.* (1983) also studied the toxicity of formaldehyde in F-344 rats exposed, for 26 weeks, 7 days per week, 22 hours per day, to concentrations similar to those used in the Cynomolgus monkey experiments. With the rats, each of the five groups was comprised of 20 males and 20 females. Squamous metaplasia type lesions of the nasal wall were observed in this study only for exposures at 2.95 ppm. Other effects, such as weight loss, were equally observed during this study.

In the same study as the one previously summarized in Section 1.1.1 for severe effects, Woutersen *et al.* (1987) also studied, in male and female Wistar albino rats exposed 6 hours per day, 5 days a week for 13 weeks (subchronic exposure) to 0, 1, 10 or 20 ppm of formaldehyde, the effects on the nasal epithelium. The groups were then made up of ten animals, euthanatized 18 hours after the end of their exposure. The lesions observed at 10 ppm included moderate squamous metaplasia of the nasal epithelium, whereas exposure to up to 1 ppm of formaldehyde did not permit conclusions as to its cytotoxic potential or not.

Woutersen *et al.* (1989) studied the effects on a damaged nasal mucosa of subchronic (3 months) and prolonged (28 months) exposure to formaldehyde in Wistar rats. 720 male rats were used; they were divided into 16 groups of animals allowing for testing at 4 levels of exposure (0, 0.1, 1 and 10 ppm for 3 months and for 28 months in 2/3 of the rats with a damaged nasal mucosa and 1/3 of the rats with an intact nasal mucosa). In the rats without a damaged nasal mucosa, no histopathological change was observed in the groups exposed to from 0.1 to 1 ppm for 3 months. However, exposure at 10 ppm led to the observation of an increase in the incidence of squamous metaplasia and rhinitis in rats with intact noses, as well as an increase in the incidence of rhinitis and histopathological changes such as squamous metaplasia, hyperplasia of the basal or pseudo-epithelial cells, thinning and disorganization of the olfactory epithelium in rats who had a damaged nose.

The effects of formaldehyde on the nasal epithelium were studied by Zwart *et al.* (1988) in male and female Wistar rats. Four groups of 50 males and 50 females were each exposed for 13 weeks to levels of 0, 0.3, 1 and 3 ppm for 5 days per week, 6 hours per day and the tissues of their nasal cavities examined for any histopathological changes. Several changes were observed in most of the rats exposed to the highest dose (3 ppm), and they included disorganization and hyperplasia of the cells of the respiratory epithelium, squamous metaplasia of the front part of the nose normally covered by cells of the respiratory epithelium. A proliferation of nasal cells, which increased according to the dose, was observed (even if it was less after 13 weeks than after 3 weeks of exposure), as well as a cellular renewal that was significantly greater in the most exposed group in relation to the control subjects. There was no difference, however, in the latter point for the groups with the lowest exposures.

Renal Effects due to Subchronic Exposure in Animals

Only one animal study seems to deal with it, which is the Appelman *et al.* (1988) study. These authors observed a significant difference in the frequency of oligury among male Wistar rats without nasal damage, by electro-coagulation, exposed for 6 hours per day, 5 days per week for 52 weeks to 10 ppm of formaldehyde ($p<0.05$). This involved male rats without nasal damage that were exposed the longest and most heavily. This effect did not prove to be significant in rats that were exposed the longest and most heavily but who had suffered nasal damage.

Effects such as Weight Loss due to Subchronic Exposure in Animals

At least five animal studies report information relative to this type of effect.

First of all, Appelman *et al.* (1988), in their study on Wistar rats indicated a retarding of growth in rats both with and without nasal damage after two weeks of exposure at 10 ppm of formaldehyde for 5 days per week and 6 hours per day. For the authors, the other effects, such as weight loss, observed in their study, cannot be connected to the treatment.

As for Rusch *et al.* (1983), they did not notice any significant weight loss even in their Cynomolgus monkeys exposed for 26 weeks, 7 days per week, 22 hours per day at the highest concentration in their study, namely 2.95 ppm.

As we reported in the preceding summary of the Rusch *et al.* (1983) study concerning respiratory effects, other effects such as weight loss were observed in F-344 rats, exposed for 26 weeks, 7 days per week, 22 hours per day to various levels of formaldehyde. In fact, it is at the highest level encountered in this study, (namely 2.95 ppm) that weight loss in males (-14.4%) as well as in females (-11.2%) was observed.

In the Woutersen *et al.* (1989) study previously summarized for the subchronic respiratory effects that affected the male Wistar rats exposed for 3 months, 5 days per week, 6 hours per day, a retarding of growth was noted as of the 14^{th} day of exposure for the group most strongly exposed (at 10 ppm of formaldehyde). The authors indicated that in the least exposed groups, the weight of the animals without damaged nasal mucosa was generally slightly less that those whose nasal mucosa had been damaged, as compared to the control group.

Zwart *et al.* (1988) reported no effect of this type regardless of the level of exposure tested during their subchronic experimentation on male and female Wistar rats exposed by inhalation for 13 weeks, 5 days per week, 6 hours per day.

Effects on Reproduction due to Subchronic Exposure in Humans

Ward *et al.* (1984) were interested in knowing if exposure to formaldehyde could cause effects such as morphological or quantitative change in sperm in a group of workers in a hospital autopsy department. 11 exposed individuals and 11 non-exposed individuals, matched according to sex, age, alcohol, tobacco and marijuana consumption habits, were recruited. The periods of exposure were all greater than 1 month, and the estimated average exposure between 0.61 and 1.32 ppm. No statistically significant difference was shown between the exposed and the non-exposed. Nevertheless, according to the authors, the absence of effect could be due to the study's lack of statistical power.

Carcinogenic Effects due to Subchronic Exposure in Humans

In order to evaluate the carcinogenic effects of formaldehyde in humans, Stayner *et al.* (1988) performed a study of mortality on a retrospective population of workers exposed for at least three months in the three clothing factories considered. A total of 11,030 workers contributing for 188,025 people - years were included. The vital status of the individuals was traced back as far as 1982 for 96% of the individuals. NIOSH (*National Institute of Occupational Safety and Health)* had taken, in each of the three factories, some formaldehyde exposure measurements, between 1981 and 1984, whose average was 0.15 ppm. The authors indicated however that this exposure could have been higher for the previous years. In general, death from non-malignant causes proved to be lower than expected. However, a significant increase in deaths from cancer of the oral cavity (SMR= 343) and the conjunctive tissues (SMR= 364) was observed. On the other hand, SMRs greater than 100, but not statistically significant, were noted for cancers of the trachea, bronchial tubes and lungs (SMR=114), the pharynx (SMR=112), the bladder (SMR=145), leukemia (SMR=113) and other neoplasms of the lymphopoietic system (SMR=170). Deaths from cancer of the trachea, bronchial tubes and lungs proved to be inversely related to the duration of exposure and the period of latency, which is contrary to what is expected with a positive dose-response relationship. Nevertheless, all these results are based on small numbers, confounding factors not considered are likely to exist, and there are obvious limitations concerning the levels of exposure.

Respiratory Effects due to Chronic Exposure in Animals

Kerns *et al.* (1983) studied the effects of long-term exposure to formaldehyde by inhalation in male (n=120) and female F-344 rats (n=120) and male and female B6C3F1 mice (n = 2 x 120) exposed for 24 months, 5 days per week, 6 hours per day at levels of 0, 2, 5.6 and 14.3 ppm of formaldehyde. Each of the 4 exposure groups was made up of 30 animals by sex and by species. Initially meant as a study of the carcinogenic potential of formaldehyde, this study allowed them to show chronic respiratory effects other than cancer. Rhinitis, epithelial dysplasia and squamous metaplasia of the nasal epithelium were noted in all the groups of exposed rats, but only in the moderately and severely exposed groups of mice.

As for Monticello *et al.* (1996), they analyzed the role of the increase in the proliferation of cells of the nasal epithelium in the formation of nasal cancer following exposure to formaldehyde by inhalation. Towards this aim, male CDF rats (F344/CrlBr) were exposed for 24 months, 5 days per week, 6 hours per day to 0, 0.7, 2, 6, 10 or 15 ppm of formaldehyde. These groups were each made up of 90 or more animals. The result of this study was that

formaldehyde induced squamous cell carcinoma in a non-linear manner (squamous metaplasia): with a threshold at 2 ppm (not statistical; no animal out of 96), a minimal response at 6 ppm (not statistical, 1 animal out of 90) and a drastic increase at 10 (20 animals out of 90) and 15 ppm (69 animals out of 147). The incidence of nasal tumors was 1%, 22% and 47% in the groups exposed to 6, 10 and 15 ppm respectively. The authors concluded that the size of the population of target cells and the sustained increase in their cellular proliferation, determined by the regional differences due to the passage of formaldehyde-contaminated air on these sites, were the factors which, coupled with a known non-linear kinetic of formaldehyde in its links with DNA, could explain the non-linearity and specificity of the sites affected by the induction of carcinoma of the squamous cells of the nose in rats.

As we previously indicated, the Woutersen *et al.* (1989) study was carried out to analyze both the subchronic and chronic effects of exposure to formaldehyde in male Wistar rats. Some rats, with and without previously damaged nasal mucosa, were exposed for 28 months, 5 days per week, 6 hours per day to formaldehyde in order to study its potential to induce nasal tumors. After 28 months of exposure, noses not previously damaged did not show any histopathological changes at the weakest concentrations of 0.1 and 1 ppm. An increase in the incidence of squamous metaplasia, of hyperplasia of the basal or pseudoepithelial cells of the nasal mucosa, and thinning and disorganization of the olfactory epithelium and rhinitis were noted for the highest exposure of 10 ppm. But regardless of the level, in rats whose mucous membranes had been damaged, exposure to formaldehyde had led to the observation of squamous metaplasia.

Effects Such as Weight Loss due to Chronic Exposure in Animals

The observation made in the Woutersen *et al.* study (1989) for the subchronic exposure also holds for the chronic part of their analyses, namely a lag in growth starting on the 14th day of exposure was noted for the most heavily exposed group (at 10 ppm of formaldehyde). As we already reported, the authors indicated that in the most highly exposed groups, the weights were generally slightly less in animals without damaged nasal mucosa than in those with damaged nasal mucosa, as compared to control subjects.

Carcinogenic Effects due to Chronic Exposure in Animals

As indicated in the section relative to respiratory type systemic chronic effects observed in animals, Kerns *et al* (1983), in a study whose initial objective was the analysis of potential carcinogens in formaldehyde, were able to show evidence of the appearance of carcinomas in squamous cells in the nasal cavity in F-344 rats exposed for 24 months, 5 days per week, 6 hours per day to 2 ppm of formaldehyde. Moreover, the inhalation of formaldehyde also seemed to be associated with an increase in the frequency of polyploid adenomas in the nasal cavity of male rats. These effects were observed in a significant manner in mice (only two male mice exposed to 14.3 ppm of formaldehyde developed squamous cell carcinomas).

Respiratory Effects due to Chronic Exposure in Humans

Alexandersson and Hedenstierna (1989) followed a group of employees exposed, between 1980 and 1985, to formaldehyde in the lumber industry (n=47) and 20 non-exposed individuals, in order to determine if the effects on the respiratory function were transitory or not. The median level of exposure to formaldehyde measured was 0.34 ppm (0.42 mg/m³) in 1980 and 0.41 ppm (0.50 mg/m³) in 1985. Nevertheless, little information is furnished on the collection of this environmental data. The spirometric tests were done in 1980 on the Monday before they resumed work as well as during the workday. Five years later, 18 of 20 non-exposed subjects were reexamined. Out of 47 subjects initially exposed only 21 were reexamined since 13 were excluded for various reasons (retirement, change in employment and type of exposure, lost from sight) and 13 others were no longer exposed. The data relative to the pulmonary function were compared for all subjects to reference levels adjusted for age, gender, size and weight. The exposed workers showed a significant drop in their FVC and FEV levels ($p<0.05$) during their first examination. The second evaluation 5 years later did not show any additional decline. In exposed non-smokers, the respiratory function was significantly altered during work periods, but not in smokers, who showed practically no improvement in their pulmonary function during rest periods. For the authors, this study showed evidence of temporary effects on the respiratory function during work periods with a cumulative effect over the years. The changes observed seemed nevertheless reversible after 4 weeks absence of exposure.

Boysen *et al.* (1990) evaluated the histological changes in the squamous nasal mucosa of workers occupationally exposed to formaldehyde. Nasal biopsies were carried out on 37 workers exposed to formaldehyde for 5 years or more who were paired with 37 control subjects (non-exposed). The biopsies of the exposed workers showed more metaplasic lesions than those not exposed. Also, three cases of epithelial dysplasia were observed in the exposed group. For the authors, these observations indicated that formaldehyde could potentially be carcinogenic in humans. However, given the multitude of inconclusive epidemiological studies, the results of this study tend to show, again according to the authors, the slight carcinogenic potential of formaldehyde, but also that exposure solely to formaldehyde is probably insufficient to induce nasal cancer. The levels of exposure prior to 1980 are not known. They were reconstructed based on i) the measurements taken afterward, ii) the knowledge of processes, and iii) the subjective observation of the workers. The levels thus determined varied from 0.5 to more than 2 ppm.

Edling *et al.* (1988) analyzed the cytotoxic effect of formaldehyde on the nasal membranes of 75 men who had professional exposure to formaldehyde or to formaldehyde and wood dust. The workers who accepted to participate in the study (72% out of 104 initially approached), had a medical exam as well as nasal biopsies in order to study the occurrence of early signs of the irritating effects and histopathological changes in the nasal mucosa. These individuals had been exposed to formaldehyde for 10.5 years on average, and between 1 year and 39 years maximum. No environmental measures were available before 1975, but some measures were taken between 1975 and 1983, which indicated that the levels of formaldehyde varied between 0.1 and 1.1 mg/m³ (or 0.08 and 0.9 ppm) with extremes values of up to 5 mg/m^3 (or 4.07 ppm). It is suspected that these levels were greater in the 1960s than at the beginning of the 1970s. Moreover, out of this population of 75 individuals of the average age of 38 (from 22 years to 63 years old), 36 (35%) were smokers, 7 (9%) were ex-smokers before stopping around 10 years ago, and 42 (56%) had never smoked. The control group

(non-exposed) was made up of 25 individuals of the average age of 35 years (from 25 to 60 years of age) including 12 smokers (48%), 4 ex-smokers (10%), and 9 non-smokers (36%). Among the observations made in this study, 60% of the individuals exposed to formaldehyde reported symptoms of nasal discharge or produced crusts, and 75% complained of watery eyes when they were exposed to formaldehyde. Whereas the clinical examination indicated a normal nasal mucosa in 75% of cases, the biopsies showed that only 3 of the workers showed normal nasal epithelium. For the others, there were noted losses of ciliated cells, hyperplasia of goblet cells, squamous metaplasia and slight dysplasia. According to the authors, the results of this study indicate that occupational exposure to formaldehyde at levels that vary from 0.08 and 0.9 ppm can cause histo-pathological changes in nasal mucosa compared to non-exposed persons.

In their study, Garry *et al.* (1980) were interested in the effects on health of exposure to formaldehyde in residents of Minnesota. The population studied included 275 individuals suspected of having been exposed to formaldehyde, who had been reported to the Minnesota Department of Health between February and June 1979. All these individuals were given a medical examination followed by, for some of them, a visit to their homes including a questionnaire with environmental questions (such as the age or type of home, as well as the type of insulation and heating) and a measurement of ambient levels of formaldehyde (two samples for 30 minutes in the bedroom and in the living room). Three age strata were considered: newborns to 2 years old (24 boys, 12 girls), 3 years to 13 years of age (21 boys and 9 girls), adolescents to adults (48 men and 54 women). The concentrations of formaldehyde varied depending of the season, and oscillated between 0.1 and 3 ppm. All age groups reported irritating effects on the eyes, the nose and the throat, as well as coughing, wheezing and other respiratory problems. Asthmatic individuals reported symptoms at levels lower than non-asthmatics. As for smokers, they seemed to be much less sensitive to the irritating effects of formaldehyde. As an essential criticism of this study we should note the possibility of confounding factors not taken into consideration as well as the absence of a control group and absence of information on the duration of the exposure, and a questionnaire that can probably have a subjective effect.

Holness and Nethercott (1989) examined the effects of exposure to formaldehyde on the respiratory and cutaneous tissues of workers in funeral services in Canada. Eighty four workers (directors and apprentices) out of 97 potentials were recruited and compared to 38 control subjects including individuals from a large service organization but also students who were paid to participate. The levels of formaldehyde noted during embalming were 0.36 ppm on the average with a standard deviation of 0.19 ppm (range of 0.08 to 0.81 ppm). The individuals recruited answered a questionnaire, and underwent several pulmonary and dermal tests (patches). The funeral services workers had been employed in the industry on the average for 8.2 years with a standard deviation of 9.9 years. This study showed evidence that the symptoms reported (chronic bronchitis, dyspnea, irritation of the eyes, nose and skin) were more frequent with the embalmers than with the control group. However, no significant effects on FVC, FEV_1, $FEF_{50\%}$ or $FEF_{75\%}$ were shown between the exposed and the non-exposed group. The patches also showed evidence that 10% of the exposed individuals were sensitive to formaldehyde as compared to none of the control subjects.

Horvath *et al.* (1988) studied 109 fiberboard and molded plastics workers and 254 control subjects and the effects of formaldehyde on the mucous membranes and lungs. A questionnaire regarding the respiratory symptoms experienced, as well as spirometric tests, were applied before and after the workday. The levels of exposure were determined for each of the subjects tested and varied between 0.17 ppm and 2.93 ppm (average of 0.69 ppm). As concerns the duration of exposure, it was 10.3 years on average (from less than one year to 20 years). It should be noted that, for the fiberboard production area, particles from soft wood were also present in the ambient air. The prevalence of respiratory symptoms after one day of work were higher in those exposed than in the non-exposed for coughing (35% vs. 19%), pulmonary distress (9% vs. 2%), the production of mucous (27% vs. 10%), burning sensation in the nose (28% vs. 2%), nasal congestion (34% vs. 14%), nasal itching (21% vs. 8%) and dry or burning throat (22% vs. 3.9%). Nevertheless, the results of spirometric tests before exposure were similar in the two groups but showed a significant lessening for the exposed group after the workday. No difference in the pulmonary function was noted between smokers and non-smokers. The authors concluded that formaldehyde could be at the origin of small changes in pulmonary functions during the workday, but these changes did not affect the pulmonary function in a permanent manner.

We should note that among the studies that looked at systemic respiratory effects due to chronic exposure, and where the levels of exposure to formaldehyde were less than or equal to 2 ppm, at least two reported no effects, that of Nunn *et al.* (1990) and that from Schachter *et al.* (1987). The first of these two negative studies (Nunn *et al.,* 1990) involved 164 workers exposed to formaldehyde each day during the production of formaldehyde urea resin compared to 129 non-exposed workers examined for various parameters relative to the respiratory function. These workers were examined between 1980 and 1986, and their tobacco habits were also monitored. The second study (Schachter *et al.,* 1987) involved hospital laboratory workers regularly exposed to formaldehyde between 1 and 21 years, 1 to 7 days per week. However, there did not seem to be any real control group in the protocol presented. The subjects were exposed in double blind and at random to concentrations of 0 to 2 ppm of formaldehyde for 40 minutes with or without moderate exercise for 10 minutes (four study periods considered: 0 ppm with or without moderate exercise and 2 ppm with or without moderate exercise). Some slight and temporary symptoms were reported such as abnormal odor and eye irritation, but no effect on the lower respiratory tract (bronchial tubes and bronchioles) was reported and no effect on the respiratory function was in evidence.

Musculoskeletal effects due to Chronic Exposure in Humans

The Holness and Nethercott study (1989), carried out on 84 embalmers and apprentice embalmers in Canada and described earlier for the systemic respiratory effects, is one of the rare studies to have reported that 23% of exposed workers compared to 5% of control subjects exhibited muscular or articular stiffness.

Effects on Reproduction due to Chronic Exposure in Humans

In their study of 275 residents in Minnesota of which 77 were women, Garry *et al.* (1980) determined a rate of miscarriage of 11.6% which, according to them, did not differ from that reported in the studies done in non-exposed populations. Compared to the population of childbearing age, according to the data furnished by the authors, this rate is 16.7% (54 women, approximately 9 miscarriages). The rate of premature birth observed was 11.7%, a little higher than that normally observed in these populations, but lower than that for black women. According to the authors, these observations thus are not conclusive.

Carcinogenic Effects due to Chronic Exposure in Humans

As we indicated in the introduction, the objective of this preliminary study is to analyze if the available data actually allows us to estimate with acceptable precision the "dose-response" relationship for toxic effects of concentrations of 2, 1, 0.75 or 0.3 ppm. This should not however allow us to forget that from a "danger identification" point of view, numerous studies have fueled the debate around the carcinogenic effects of formaldehyde in humans, and even if they only have a limited impact. The IARC (1995) in its monograph on wood dust and formaldehyde indicate moreover that an increase in cases of nasopharyngeal cancer have been associated with exposure in two of the six studies involving groups of workers occupationally exposed, as well as in three out of four case studies and in the meta-analyses. Even if it seems, still according to the group of experts from the IARC, that the associations observed between exposure to formaldehyde and the risk of nasopharyngeal cancer cannot be attributed to other contaminants, including wood dust or tobacco use, these studies remain of essentially limited extent for reasons of improper classifications of exposure or illnesses, or for those who were lost from sight. As concerns nasal cancer (nasal cavity and paranasal sinuses), three case studies out of six available reported increases whereas the population studies do not show any increases. No study has shown evidence of increased risk of oropharyngeal, laryngeal or lung cancers. Overall, the IARC group of experts considers that all the epidemiological studies do not fully prove that formaldehyde is a carcinogen in humans, but rather provide limited proof, principally on the basis of nasopharyngeal cancers and to a lesser extent cancers of the nose. This having been specified, the two studies that we are presenting here on humans, are the two studies for which the documented exposure shows levels in the area of the small doses that interest us here.

Gérin *et al.* (1989) carried out a case-control study in order to assess the possible relation between exposure to formaldehyde and various types of cancer (oesophageal, stomach, colorectal, liver, pancreas, lung, prostate, bladder, kidney, melanoma and lymphoid tissues). The incidence of cases of cancer was recorded in the male population aged between 35 and 70 years old, between September 1979 and December 1985. A total of 4,510 eligible cases were identified, of which 3,726 completed interviews or questionnaires (around 83%). The control group for each type of cancer was made up i) of 533 men selected from voting lists and stratified according to age, in accordance with the distribution of ages in the cases that had agreed to participate out of 740 at the beginning, and was completed ii) by "control" cancer patients suffering from a cancer other than the one in the study. Nevertheless, the individuals with lung cancer were not in any control group. After reconstructing the potential exposure to formaldehyde, three groups were defined: less than 0.1 ppm, from 0.1 to 1 ppm and more than 1 ppm. The period of exposure varied between 1 and 20 years. Logistical regressions for each type of cancer were then carried out. These logistical regressions were

adjusted for 5 confounding factors *a priori,* either age, belonging to ethnic groups, socio-economic status, tobacco use, and the "cleanliness" of the work of the individual. In case by case, other confounding factors may have been included in the logistics. No significant odds-ratio was determined; only an OR proved to be greater than 2, that of adenocarcinoma of the lungs with a non significant OR of 2.3 obtained for the most exposed group (confidence interval = 0.9-6). However, as the authors reported, the possibility of a slight increase in the risk cannot be excluded. In addition, the protocol for the study (control-case group), which included cases and control subjects of various professional backgrounds, makes it even more difficult to evaluate the exposure. Thus, as the authors indicated, very few subjects were exposed to average levels greater than 1 ppm. Finally, it should be noted that the types of cancer of the upper respiratory tract (nose, pharynx) were not included in this study.

The study by Stayner *et al.* (1985a, 1985b) also had the objective of assessing the carcinogenic potential of formaldehyde. It was a study of the proportionate mortality ratio (PMR) as well as a study of the proportionate cancer mortality ratio (PCMR). Such studies thus assume to determine the proportionate mortality ratios that are obtained by dividing the number of deaths observed for a specific cause by the number of deaths expected based on the proportion of deaths of this category in the general population. 256 deaths of workers at the three clothing factories were included in this study. The three factories have used manufacturing procedures using formaldehyde since 1958, and the duration of employment of the group of individuals studied averaged 9.4 years. Environmental measurements taken at the beginning of the 80's in 2 of the 3 factories showed levels of formaldehyde varied between 0.1 and 1 ppm. Although no data on environmental concentrations was available prior, these were nevertheless suspected to be greater than those noted after improvements in the resin system, improvements which were likely to have strongly diminished the levels of formaldehyde present in the clothing. Several significant instances of increased mortality were shown for cancer of the oral cavity (PMR=750), cancer of the biliary and hepatic passages (PMR=313), as well as for cancer of the lymphatic and hematopoietic areas (PMR=400). By limiting the analysis to deaths by cancer only, we obtain the proportionate cancer mortality ratios (PCMR). These were also shown to be higher for the oral cavity (PCMR=682), the biliary and hepatic passages (PCRM=274), as well as for lymphatic and hematopoietic areas (PCMR=342). For the authors, given the few deaths in each of the categories and the lack of consistency with the results of other studies, the degree of confidence to give to these PMRs is limited. Nevertheless, according to them, the fact that the excess deaths were noted in workers with a long period of latency (greater than 10 years) and exposure, and that no other known environmental factor can explain the observations noted, tends to support the hypothesis that these excess deaths are associated with exposure to formaldehyde.

Existing NOAEL and LOAEL

Here we go back to the various NOAEL and LOAEL for less significant effect and significant effect determined by the ATSDR (1999) for each of the studies that reported levels of formaldehyde less than or equal to 2 ppm, while we endeavor in any case to show levels of confidence in the interpretations of the ATSDR which are very rarely justified. By definition, an LOAEL for less serious effect corresponds to a level of exposure that should not be able to induce effects that are likely to cause serious dysfunction or death. These NOAEL/LOAEL from the ATSDR are not necessarily defined on a statistical basis. It may at times be a case of NOAEL/LOAEL defined solely on a "biological" basis, which is not specified by the ATSDR. Moreover, we should recall that the level of 2 ppm corresponds to the actual value of permissible ceiling exposure levels in Quebec, and that given that the multitude of existing inhalation studies and the objective of revision to lower this level, only the studies showing levels lower than or equal to this level are presented here for animals as well as humans. NOAEL and LOAEL sometimes greater than this can sometimes be shown when the studies concerned show several levels of exposure, where at least one of them was less than or equal to 2 ppm and involved the absence or the presence of relevant effects.

Existing NOAEL and LOAEL in Animals

On the following Table No. 1, we can note that for the severe effects, only one study stands out from among the 7 presented here due to its protocol and the number of animals involved. This study (Monticello *et al.,* 1991) allows us to determine a NOAEL in male F-344 rats of 2 ppm and an LOAEL for significant effect of 6 ppm.

As concerns the subchronic effects and if only the studies that show a high confidence level are considered, the highest NOAEL would be 3 ppm (loss of weight in the Zwart *et al.* (1988) study) and the lower LOAEL also of 3 ppm for a less significant effect (obtained again from the Zwart *et al.* (1988) study), and of 6 ppm for a significant effect (obtained from the Monticello *et al.,* (1991) study).

Table 1: NOAEL / LOAEL in the Animal Studies Presented

Effects	Species, sex	NOAEL[+]	LOAEL[+]		Reference	Confidence level*
			Less significant	Significant		
Severe						
Systemic Respiratory	Rats ♂ F-344		2		Chang *et al.* (1981)	Low
	Mice ♂ B6C3F1		2			Low
	Rats ♂ F-344	2	6		Montiero-Riviere and Popp (1986)	Low
	Rats ♂ F-344	2		6	Monticello *et al.* (1991)	High
	Rats ♂ F-344	2	15		Morgan *et al.* (1986a)	Low
	Rats ♂ F-344	0.5	2	6	Morgan *et al.* (1986b)	Low
	Hartley Guinea Pigs	0.5	1.05		Swiecichowski *et al.* (1993)	Low
	Rats ♂ and ♀ Wistar	1	10		Woutersen *et al.* (1987)	Low
Subchronic						
Systemic Respiratory	Rats ♂ Wistar	1	10		Appelman *et al.* (1988)	Medium
	Rats ♂ F-344	2	6		Casanova *et al.* (1994)	Low
	Mice ♂ B6C3F1	2		4	Maronpot *et al.* (1986)	Low
	Mice ♀ B6C3F1	4		10		Low
	Rats ♂ F-344	2		6	Monticello *et al.* (1991)	High
	Cynomolgus Monkeys ♂	0.98	2.95		Rusch *et al.* (1983)	Low
	Rats ♂ and ♀ F-344	0.98	2.95			Medium
	Rats ♂ and ♀ Wistar	1	10		Woutersen *et al.* (1987)	Low
	Rats ♂ Wistar	1	10		Woutersen *et al* (1989)	High
	Rats ♂ and ♀ Wistar	1	3		Zwart *et al.* (1988)	High
Systemic Renal	Rats ♂ Wistar	1		10	Appelman *et al.* (1988)	Medium
Weight loss type	Rats ♂ Wistar	0.1	10		Appelman *et al.* (1988)	Medium
	Cynomolgus Monkeys ♂	2.95			Rusch *et al.* (1983)	Low
	Rats ♂ and ♀ F-344	0.98	2.95			Medium
	Rats ♂ Wistar	1	10		Woutersen *et al.* (1989)	High
	Rats ♂ and ♀ Wistar	3			Zwart *et al.* (1988)	High

Chronic						
Systemic Respiratory	Rats ♂ and ♀ F-344			2	Kerns *et al.* (1983)	High
	Mice ♂ and ♀ B6C3F1	2	5.6			High
	Rats ♂ CDF	2	6		Monticello *et al.* (1996)	High
	Rats ♂ Wistar	1	10		Woutersen *et al.* (1989)	High
Weight loss type	Rats ♂ Wistar	1	10		Woutersen *et al.* (1989)	High
Carcinogens	Rats ♂ and ♀ F-344			2	Kerns *et al.* (1983)	High

[+] in ppm of formaldehyde
** in comparison to ATSDR (1998) conclusions, taking into account in particular the size of the groups (≤10: low [11 to 30]: medium ≥30: high)

As for the chronic effects, all the experimental studies that are involved seem to present relevant protocols and include a satisfactory number of animals. Among these studies, the highest NOAEL of 2 ppm was obtained by Kerns *et al.* (1983) and Monticello *et al.* (1991), whereas the lowest LOAEL of 5.6 ppm for less significant effect was obtained from the Kerns *et al.* (1938) study, like that of 2 ppm for significant effect.

Existing NOAEL and LOAEL in Humans

As concerns the human studies, only an in-depth analysis of the protocols based on strict criteria previously defined would allow for establishing a categorical confidence level of the type defined in the animal data. Each study in effect shows its own particularities that make such an exercise much more complex and long winded. This is why we preferred at this stage to abandon such a qualitative classification. Let us note however that none of the studies has clearly stood out whether it was about the acute, subchronic or chronic effects. They all have points that can be criticized, which are likely to produce uncertainty that is as qualitative as it is quantitative regarding the observations reported.

On Table No. 2, we note that in humans and for the severe effects due to exposure to formaldehyde, the highest NOAEL is 3 ppm and was determined in the Reed and Frigas study (1985), whereas the lowest LOAEL for less significant effect is 0.41 ppm and was determined in the Pazdrak *et al.* (1993) study relative to systemic respiratory type effects, but also by the Gorski and Krakowiak (1991) study for immunological and lymphoreticular type effects. We should note that no LOAEL, for significant effects has been proposed by ATSDR (1999) on the basis of these studies.

As concerns subchronic effects, the only NOAEL available is at 1.32 ppm (absence of effect on the sperm) and was obtained from the Ward *et al.* (1984) study, whereas the only LOAEL available is at 0.15 ppm. This LOAEL is related to the carcinogenic effects noted in the Stayner *et al.* (1988) study, which, however, has many limitations.

To finish, at the levels that interest us here (less than or equal to 2 ppm), two epidemiological studies have led the ATSDR to define the LOAEL for significant cancer-type effects. It involves the study by Gérin *et al.* (1989) and by Stayner *et al.* (1985a, 1985b). For the

ATSDR (1999), these studies allow us to determine an LOAEL of less than 1 ppm in the first case, and an LOAEL that would be between 0.1 and 1 ppm in the second. However, many limitations are attached to these studies, which render the conclusions of the ATSDR (1999) very open to criticism at the very least.

Table 2: NOAEL / LOAEL in the Human Studies Presented.

Effects	Gender	NOAEL[+]	LOAEL[+]		Reference
			Less significant	Significant	
Acute					
Systemic Respiratory	♂ (?)	0.41			Gorski *et al.* (1992)
	♂ and ♀		3		Green *et al.* (1987)
	♂ and ♀	0.70			Harving *et al.* (1990)
	♂ and ♀		2		Kulle *et al.* (1987)
	♂ and ♀		2		Nordman *et al.* (1985)
	♂ and ♀		0.41		Pazdrak *et al.* (1993)
	♂ and ♀	3			Reed and Frigas (1984)
	♂ and ♀		3		Sauder *et al.* (1986)
	♂ and ♀		3		Sauder *et al.* (1987)
	♂ and ♀		2		Schachter *et al.* (1986)
	♂ (?)		2		Witek *et al.* (1986)
	♂ and ♀		2		Witek *et al.* (1987)
Systemic Hematological	NS	1			Pross *et al.* (1987)
Immunological over/ Lymphoreticular	♂ (?)		0.41		Gorski *et al.* (1992)
	NS	1			Pross *et al.* (1987)
Subchronic					
Reproductive	♂	1.32			Ward Jr. *et al.* (1984)
Carcinogens	♂ and ♀			0.15	Stayner *et al.* (1988)
Chronic					
Systemic Respiratory	♂ (NS)		0.34		Alexanderson and Hedenstierna (1989)
	♂ (NS)		0.50		Boysen *et al* (1990)
	♂		0.08		Edling *et al.* (1988)
	♂ and ♀		0.1 – 3		Garry *et al* (1980)
	♂ and ♀		0.36		Holness and Nethercott (1989)
	♂ and ♀		0.69		Horvath *et al* (1988)
	♂	2			Nunn *et al.* (1990)
	♂ and ♀	2			Schachter *et al.* (1987)
Systemic Musculo-skeletal	♂ and ♀		0.36		Holness and Nethercott (1989)
Reproductive	♀	3			Garry *et al.* (1980)
Carcinogens	♂			< 1	Garry *et al.* (1989)
	♂ and ♀			0.1 – 1	Stayner *et al.* (1985a, 1985b)

NS: non specified
+ in ppm of formaldehyde

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Appendix 2: The relationship between exposure to formaldehyde and cancer of the upper respiratory tract in humans (extract from the work by Sandra Fradet)

Analysis of Case-Control Studies

18 case-control studies were selected and analyzed. A summary of each study and the corresponding comments are given in Table 1.

Table 1. Presentation and analysis of case-control studies
OR = odds ratio; CI = confidence interval

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Brinton *et al.*, 1984	**Sinus and nasal cavities**	- Exposure to formaldehyde	OR: 0.35 (0.1-1.8)	• Lacks power; few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. Interviews conducted by telephone. No direct measurement or mention of concentration. Possible memory bias during interview, although less important in the hospitalized control group. • Average participation (83% of cases and 78% of controls). • Approx. 35% of interviews were conducted directly with subjects; the rest of them were conducted by a close family member. • Incident cases from 4 American hospitals. • Possibility that another uncontrolled factor may contribute to the observed risk. The authors conducted a multi-variate analysis that used a logistic probability model to simultaneously control for a variety of potential confounding variables. The authors collected data on several possible confounding factors as well as several other chemical substances.

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Olsen *et al.*, 1984	**Sinus and nasal cavities**	- Exp. (men) - Exp. (women) - Exp. (men) w/out exp. to wood dust - Exp. (men) with exp. to wood dust	OR = 2.8 (1.8-4.3)* OR = 2.8 (0.5-14.3) OR = 1.8 (0.7-4.9) OR = 3.5 (2.2-5.6)*	• Lacks power: few cases and low proportion of people exposed to formaldehyde. Most of those exposed to FM were also exposed to wood dust. • Possible misclassification of exposure. Three industrial hygienists classified the probability of exposure from data available in the Danish supplementary pension fund. All employees in the country are listed there with various data on employment since 1964. Memory and selection bias significantly reduced. No direct measurement. • Incident cases from the cancer registry of Denmark. • Possibility that another uncontrolled factor contributed to the observed risk. The authors stratified for exposure to wood dust to consider its possible confounding effect. No data were available on cigarette and alcohol use.
	Nasopharynx	- Exp. (men) - Exp. (women)	OR = 0.7 (0.3-1.7) OR = 2.6 (0.3-21.9)	
Vaughan *et al.*, 1986	**Oropharynx and hypopharynx**	- High exposure level (no value available) - More than 10 yrs exposure - Odds of exp. greater than 20	OR = 0.6 (0.1-2.7) OR = 1.3 (0.7-2.5) OR = 1.5 (0.7-3.0)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. Exp. matrix used. No concentration available. • Half of the interviews were conducted by a close family member for the cases, but not for the controls. Possible memory bias during interview. • Incident cases from the Cancer surveillance system, SEER, Washington State. • Possibility that another uncontrolled factor may have contributed to the observed risk. The authors used a multiple logistic regression model to test a variety of potential confounding variables and to adjust the risk estimate as needed. The authors collected data on several possible confounding factors (cigarettes, alcohol, socio-economic class) as well as on residential and occupational history.
	Nasopharynx	- Avg. or high exposure level (no value avail.) - More than 10 yrs exposure - Odds of exp. greater than 20	OR = 1.4 (0.4-4.7) OR = 1.6 (0.4-5.8) OR = 2.1 (0.6-7.8)	
	Sinus and nasal cavities	- Avg. or high exposure level (no value avail.) - More than 10 yrs exposure - Odds of exp. greater than 20	OR = 0.3 (0.0-1.3) OR = 0.4 (0.1-1.9) OR = 0.3 (0.0-2.3)	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Hayes *et al.*, 1986	Paranasal sinus and nasal cavities	- Exp. (eval. A) - Exp. (eval. B) - Exp. (eval. A) limited to low levels of wood dust - Exp. (eval. B) limited to low levels of wood dust - Exp. (eval. A) limited to low levels of wood dust (squamous cell carcinoma) - Exp. (eval. B) limited to low levels of wood dust (squamous cell carcinoma)	OR= 2.5 (1.5-4.3) ♣ * OR = 1.9 (1.2-3.0) ♣ * OR = 2.5 (1.2-5.0) ♣ * OR = 1.6 (0.9-2.8) ♣ OR = 3.0 (1.3-6.4) ♣ * OR = 1.9 (1.0-3.6) ♣	• Lacks power; few cases and low proportion of people exposed to formaldehyde. 95% confidence interval would have been more appropriate. • Possible misclassification of exposure. Two industrial hygienists independently classified (A and B) the probability and level of exposure from data available following the interviews. The two assessments differ considerably at times. Possible memory bias during interview. • Average participation (78% of cases and 75% of controls). Participation of only 64% in deceased cases and controls. • 10% of interviews were conducted by telephone for controls, but not for cases. • Incident cases from 6 institutions in the Netherlands. • Possibility that another uncontrolled factor contributed to the observed risk. The authors stratified for exposure to wood dust. According to the authors, it is extremely difficult to assess exposure to formaldehyde independently compared to exposure to wood dust. Also according to the authors, other confounding exposures may have been involved.

Note: eval. = Evaluation

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Olsen and Asnaes, 1986	Paranasal sinus and nasal cavities (squamous cell carcinoma)	- FM exp. (std adjustment for wood dust) - FM exp. (restrictive adjustment for wood dust)	OR = 2.3 (0.9-5.8) OR = 2.5 (0.9-6.8)	• Lacks power; few cases and low proportion of people exposed to formaldehyde. Most of those exposed to formaldehyde were also exposed to wood dust. • Possible misclassification of exposure. Three industrial hygienists classified the probability of exposure from data available in the Danish supplementary pension fund. All employees in the country are listed there with various data on employment since 1964. Memory and selection bias significantly reduced. No direct measurement. • Incident cases from the cancer registry of Denmark. • Possibility that another uncontrolled factor contributed to the observed risk. The authors stratified for exposure to wood dust to consider its possible confounding effect. No data were available on cigarette and alcohol use.
	Paranasal sinus and nasal cavities (adeno-carcinoma)	- FM exposure (std adjustment for wood dust) - FM exp. (restrictive adjustment for wood dust)	OR = 2.2 (0.7-7.2) OR = 2.3 (0.4-12.0)	
	Nasopharynx		No association between exposure to FM and nasopharyngeal cancer (no results presented)	
Roush *et al.*, 1987	Nasopharynx	- Probable exposure to high levels (>1 ppm) more than 20 yrs preceding death - Probable exposure to high levels (>1 ppm) more than 20 yrs preceding death, and death at over 68 yrs of age	OR = 2.3 (0.9-6.0) Bilateral, P = 0.1 OR = 4.0 (1.3-12)* Bilateral, P = .015	• Lacks power; few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. One industrial hygienist classified the probability and level of exposure from data available in death certificates and the Price & Lee directory for the city. • Incident cases from the Connecticut registry of tumors. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age at death, year of death and availability of occupation-related information. The authors did not control for several possible confounding factors (wood dust, cigarettes, alcohol, nutrition, socio-economic class).
	Sinus and nasal cavities	- Probable exposure to high levels (>1 ppm) more than 20 yrs preceding death	OR = 1.5 (0.6-3.9)	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Partanen *et al.*, 1990	All types of cancer of the respiratory tract	- Cumulative exp. ≥3 ppm/month - Repeated exp. to more than 2 ppm - Exp. >2 ppm - More than 5 yrs exp. - Cumulative exp. >5 ppm/year	OR = 1.11 (0.40-3.11) OR = 0.22 (0.03-1.48) OR = 0.97 (0.16-5.85) ♣ OR = 1.53 (0.63-3.67) ♣ OR = 0.45 (0.11-1.88) ♣	• Lacks power; very few cases. Most types of cancer of the respiratory tract were lung cancer. There were very few types of cancer of the upper respiratory tract, and these were grouped together. • Possible misclassification of exposure. Exp. matrix used. Cases and controls from a cohort study for which exposure had already been characterized. Classification was probably higher than classification by questionnaire. Non-differential classification. • Cumulative exposure was not very useful. Severity appears to be linked more to the formaldehyde concentration in the air than to cumulative exposure. It was not demonstrated that the risk of being exposed to 2 ppm for 2 yrs is the same as that of being exposed to 0.2 ppm for 20 years. • Different proportion of deceased persons in cases (90%) and controls (33%). Possible memory bias during interview. • Incident cases from the Finland cancer registry, from a cohort study. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a conditional logistic regression model to estimate the risk by controlling for cigarette use and/or vital status. The authors did not control for several possible confounding factors (wood dust, alcohol, nutrition, socio-economic class). • No dose-response relationship was observed. An inverse relationship was often found.
	Upper respiratory tract	- Cumulative exp. ≥3 ppm/month (not adjusted for cigarettes)	OR = 2.38 (0.43-13.2) ♣	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Merletti *et al.*, 1991	Oral cavity and oropharynx	- FM exposure - Probable or definite FM exposure	OR = 1.6 (0.9-2.8) OR = 1.8 (0.6-5.5)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. Exp. matrix used to assess the probability and level of exposure. No direct measurement. No specific concentration available. Possible memory bias during interview. • Participation differed between cases and controls (approx. 83% for cases and 57% for controls). • Incident cases from the city of Turin, Italy. • Possibility that another uncontrolled factor contributed to the observed risk. The authors estimated risk by controlling for age, education level, place of birth, cigarette and alcohol consumption. • When the subjects who were exposed to formaldehyde were studied in detail, no dose-response relationship was observed. Additionally, no relationship was observed between exposure time and cancer risk.
Wortley *et al.*, 1992	Larynx	- Low exp. peak - Avg. exp. peak - High exp. peak - Exp. time ≥10 yrs - Odds of exp. greater than 20 - Avg. or high exp. level for 10 or more yrs - High exp. level for 10 or more yrs	OR = 1.0 (0.6-1.7) OR = 1.0 (0.4-2.1) OR = 2.0 (0.2-19.5) OR = 1.3 (0.6-3.1) OR = 1.3 (0.5-3.3) OR = 4.2 (0.9-19.1) OR = 4.3 (1.0-18.7)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. Exp. matrix used. No direct measurement. No specific concentration available. • 17% of interviews were conducted by a close relative for cases but not for controls. Possible memory bias during interview. • Average participation (approx. 80% for cases and controls). • Incident cases from the Cancer surveillance system, SEER, Washington State. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age, education level, cigarette and alcohol consumption. Adjustments for sex did not significantly change estimates.

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Luce *et al.*, 1993	Paranasal sinus and nasal cavities (squamous cell carcinoma)	- Avg. level ≤ 2 - Avg. level > 2 - Exp. time ≤ 20 yrs - Exp. time > 20 yrs - Cumul. exp. ≤ 30 - Cumul. exp. > 30	OR = 0.70 (0.28-1.73) OR = 1.32 (0.54-3.24) OR = 1.09 (0.48-2.50) OR = 0.76 (0.29-2.01) OR = 1.26 (0.54-2.94) OR = 0.68 (0.27-1.75)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. Most of those exposed to formaldehyde were also exposed to wood dust. • Possible misclassification of exposure. One industrial hygienist classified the probability, frequency and level of exposure from data available following interviews. No direct measurement. Possible memory bias during interviews, although less significant for the first control group as they were also patients. • Cumulative exposure was not very useful. Severity appears to be linked more to the formaldehyde concentration in the air than to cumulative exposure. • Participation low and different between groups (68% for cases, 95% for hospitalized controls and 83% for controls from known cases). • Incident cases from 27 hospitals in France. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age and sex. Other potential confounding factors were examined and included in the model as needed.
	Paranasal sinus and nasal cavities (adeno-carcinoma in men w/ avg. or high exp. to wood dust)	- Avg. level ≤ 2 - Avg. level > 2 - Exp. time ≤ 20 yrs - Exp. time > 20 yrs - Cumul. exp. ≤ 30 - Cumul. exp. 30-60 - Cumul. exp. > 60	OR = 4.15 (0.96-17.84) OR = 5.33 (1.28-22.20) * OR = 1.03 (0.18-5.77) OR =6.86 (1.69-27.80)* OR = 1.13 (0.19-6.90) OR = 2.66 (0.38-18.70) OR – 6.91 (1.69-28.23)*	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
West *et al.*, 1993	Naso-pharyngeal	- Exposure for < 15 yrs	OR = 2.7 (1.1-6.6)*	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. One industrial hygienist classified the probability of exposure from data available following interviews. No concentration available. Possible memory bias during interview. • Incident cases from general hospital in the Philippines. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a conditional logistic regression model to adjust the estimate of risk by controlling for various potential confounding factors.
		- Exposure for > 15 yrs	OR = 1.2 (0.48-3.2)	
		- < 25 yrs since first exposure	OR = 1.3 (0.55-3.2)	
		- > 25 yrs since first exposure	OR = 2.9 (1.1-7.6)*	
		- < 25 yrs at first exposure	OR = 2.7 (1.1-6.6)*	
		- > 25 yrs at first exposure	OR = 1.2 (0.47-3.3)	
Gustavsson *et al.*, 1998	Buccal cavity (squamous cell carcinoma)	- Exposure versus no history of exposure	OR = 1.28 (0.64-2.54)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. One industrial hygienist classified the probability and intensity of exposure from data available following interviews. No concentration available. Possible memory bias during interview. • Relatively good participation, but slightly different between groups (90% for cases and 85% for controls). • Most cases were questioned at the hospitals; controls were questioned at home. • Incident cases from 2 regions in Sweden. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age, geographic area, cigarette and alcohol use. It is possible that another job-related exposure may have contributed to the increase in the incidence of cancer.
	Pharynx (squamous cell carcinoma)	- Exposure versus no history of exposure	OR = 1.01 (0.49-2.07)	
	Larynx (squamous cell carcinoma)	- Exposure versus no history of exposure death	OR = 1.45 (0.83-2.51)	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
't Mannetje *et al.*, 1999	Sinus and nasal cavities	- Exposure (women) - Exposure (men) - FM and adeno-carcinoma - FM and squamous cell carcinoma	OR = 0.83 (0.41-1.69) OR = 1.66 (1.27-2.17) * OR = 3.30 (1.98-5.49) * OR = 1.27 (0.92-1.74)	• Acceptable power. Study incorporating data from 8 case-control studies. • Possible misclassification of exposure. Exposure assessment differed among the studies. Interviews conducted in each study. Exp. matrix used was developed by 2 of the study authors. No direct measurement. Possible memory bias during interview. • Cases and controls from 8 case-control studies in 5 different countries. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age, sex, study, and cigarette use, as well as for the remainder of exposures studied. According to the authors, most of the people exposed to formaldehyde were also exposed to wood dust, so it was difficult to assess formaldehyde separately. • Same weaknesses as the studies taken separately. A large proportion of the cases came from a single study: the France study. Therefore, the results of this study greatly influenced the results of the combined study.

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Vaughan *et al.*, 2000	Nasopharyngeal	- Max. exp. <0.1 ppm - Max. exp. 0.1-0.5 ppm - Max. exp. >0.5 ppm - Exp. time: 1-5 yrs - Exp. time: 6-17 yrs - Exp. time: ≥18 yrs - Cumulative exp.: 0.05-0.4 ppm/yr - Cumulative exp.: >0.4-1.10 ppm/yr - Cumulative exp.: >1.10 ppm/yr	OR = 1.4 (0.8-2.4) OR = 0.9 (0.4-2.3) OR = 1.6 (0.3-7.1) OR = 0.8 (0.4-1.6) OR = 1.6 (0.7-3.4) OR = 2.1 (1.0-4.5) OR = 0.9 (0.4-2.0) OR = 1.8 (0.8-4.1) OR = 3.0 (1.3-6.6)*	• Lacks power: few cases and low proportion of people exposed to formaldehyde. Low level of exposure. • Possible misclassification of exposure. Industrial hygienists classified the probability and level of exposure from data available following interviews. Possible memory bias during interview. • Cumulative exposure was not very useful. Severity appears to be linked more to formaldehyde concentration in the air than to cumulative exposure. • Proportion of interviews conducted by a close relative differed between cases and controls. • Incident cases from the Cancer surveillance system, SEER, in 5 populations. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used logistic regression model to test a variety of potential confounding variables and to adjust the estimate of risk as needed. • Risk increased with exposure time and cumulative exposure, but not with maximum exposure.

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Armstrong *et al.*, 2000	Nasopharyngeal	- Exposure versus no history of exposure	OR = 0.71 (0.34-1.43)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. One industrial hygienist classified the level of exposure from data available following interviews. No direct concentration available. Possible memory bias during interview. • Participation: only 53% for cases compared to 90% for controls. • Incident and prevalent cases from 4 centers with radiation therapy in the Selangor region and federal territory. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used logistic regression model to estimate risk by controlling for cigarette use and diet. Exposure to wood dust was not controlled, since, according to the authors, the OR was less than 1.5 after adjustment for diet and cigarette use.

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Laforest *et al.*, 2000	Laryngeal (squamous cell carcinoma)	- Exp. versus no exp.	OR = 1.14 (0.76-1.70)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. Exp. matrix and interviews used. No direct measurement. Possible memory bias during interviews, although less significant here given that the controls were also patients. • Cumulative exposure was not very useful. Severity appears to be linked more to the formaldehyde concentration in the air than to cumulative exposure. • Incident cases from 15 hospitals in France. • The recruitment period differed between cases (89-91) and controls (87-91). • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate risk by controlling for age, cigarette and alcohol use and, if necessary, for other professional occupations. According to the authors, it wasn't possible to assess the effect of certain known or suspected carcinogens of the larynx and pharynx, such as sulfuric acid and polycyclic aromatic hydrocarbons. • When the subjects with low probability of exposure were excluded, risk increased for hypopharynx with exposure time ($p < 0.04$) and with cumulative exposure ($p < 0.14$).
		- Prob. of exp. < 10%	OR = 1.16 (0.73-1.86)	
		- Prob. of exp. 10-50%	OR = 1.12 (0.55-2.30)	
		- Prob. of exp. > 50%	OR = 1.04 (0.44-2.47)	
		- Exp. time < 7 yrs	OR = 1.42 (0.75-2.68)	
		- Exp. time 7-20 yrs	OR = 1.09 (0.62-1.96)	
		- Exp. time > 20 yrs	OR = 0.96 (0.52-1.76)	
		- Cumul. exp. < 0.02	OR = 1.12 (0.62-2.01)	
		- Cumul. exp. 0.02-0.09	OR = 1.44 (0.79-2.63)	
		- Cumul. exp. > 0.09	OR = 0.87 (0.44-1.67)	
	Hypo-pharyngeal (squamous cell carcinoma)	- Exp. versus no exp.	OR = 1.35 (0.86-2.14)	
		- Prob. of exp. < 10%	OR = 1.08 (0.62-1.88)	
		- Prob. of exp. 10-50%	OR = 1.01 (0.44-2.31)	
		- Prob. of exp. > 50%	OR = 3.78 (1.50-9.49)*	
		- Exp. time < 7 yrs	OR = 1.09 (0.50-2.38)	
		- Exp. time 7-20 yrs	OR = 1.39 (0.74-2.62)	
		- Exp. time > 20 yrs	OR = 1.51 (0.78-2.92)	
		- Cumul. exp. < 0.02	OR = 1.03 (0.51-2.07)	
		- Cumul. exp. 0.02-0.09	OR = 1.57 (0.81-3.06)	
		- Cumul. exp. > 0.09	OR = 1.51 (0.74-3.10)	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Hildesheim *et al.*, 2001	Nasopharyngeal	- Exposure versus no exposure	OR = 1.4 (0.93-2.2)	• Lacks power: few cases and low proportion of people exposed to formaldehyde. • Possible misclassification of exposure. One industrial hygienist classified the probability and level of exposure from data available following interviews. Possible memory bias during interviews. • Cumulative exposure was not very useful. Severity appears to be linked more to the formaldehyde concentration in the air than to cumulative exposure. • Good participation: 99% for cases and 87% for controls. • Incident cases from 2 hospitals in Taipei, Taiwan. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate the association between formaldehyde and the cancer studied by controlling for age, sex and other potential confounding factors. • No significant dose-response relation was observed. In EBV positive subjects, several criteria even appeared to have an inverse relationship.
		- Exp. versus no exp (EBV positive only)	OR = 2.7 (1.2-5.9)*	
		- Exp. time ≤ 10 yrs	OR = 1.3 (0.69-2.3)	
		- Exp. time > 10 yrs	OR = 1.6 (0.91-2.9)	
		- Cumul. Exp.: < 25	OR = 1.3 (0.70-2.4)	
		- Cumul. exp.: ≥ 25	OR = 1.5 (0.88-2.7)	
		- < 20 yrs since first exposure	OR = 2.3 (0.95-5.8)	
		- ≥ 20 yrs since first exposure	OR = 1.2 (0.76-2.0)	
		- < 25 yrs at first exposure	OR = 1.3 (0.80-2.0)	
		- ≥ 25 yrs at first exposure	OR = 3.4 (0.94-12)	

Study	Types of cancer studied	Exposure to formaldehyde	Results (CI 95%) 90% CI if ♣ Significant if *	Comments
Luce *et al.*, 2002	Sinus and nasal cavities (squamous cell carcinoma)	- Low exp. – men	OR = 1.2 (0.8-1.8)	• Acceptable power. • Possible misclassification of exposure. Assessment of exposure differed between studies. Interviews conducted in all studies. Exp. matrix used developed by 4 of the study authors. Possible memory bias during interviews. Industrial hygiene data allowed semi-quantitative exposure indices to be elaborated. • Cases and controls from 12 case-control studies in 7 different countries. • Possibility that another uncontrolled factor contributed to the observed risk. The authors used a logistic regression model to estimate the association between formaldehyde and the cancer studied by controlling for age, study and sex. Other potential confounding factors were examined and included in the model as needed. According to the authors, few workers were exposed to formaldehyde that were not also exposed to wood dust, so it is possible that the residual effect of wood dust is a confounding factor. • Same weaknesses as with the studies taken separately. A large proportion of the cases came from a single study: the France study. Therefore, the results of this study greatly influenced the results of the combined study.
		- Avg. exp. – men	OR = 1.1 (0.8-1.6)	
		- High exp. – men	OR = 1.2 (0.8-1.8)	
		- Low exp. – women	OR = 0.6 (0.2-1.4)	
		- Avg. exp. – women	OR = 1.3 (0.6-3.2)	
		- High exp. – women	OR = 1.5 (0.6-3.8)	
	Sinus and nasal cavities (adeno-carcinoma)	- Low exp. – men	OR = 0.7 (0.3-1.9)	
		- Avg. exp. – men	OR = 2.4 (1.3-4.5)*	
		- High exp. – men	OR = 3.0 (1.5-5.7)*	
		- Low exp. – women	OR = 0.9 (0.2-4.1)	
		- Avg. exp. – women	---	
		- High exp. – women	OR = 6.2 (2.0-19.7)*	

Analysis of Cohort Studies

12 cohort studies were selected and analyzed. A summary of each study and the corresponding comments are given in Table 2.

Table 2. Presentation and analysis of cohort studies
PMR = proportional mortality ratio; PCMR = proportional cancer mortality ratio; SMR = standardized mortality ratio; SPIR = standardized proportional incidence ratio; RR = relative risk; CI = confidence interval; Sig. = significant

Study	Population and exposure levels	Types of cancer studied (no. of cases)	Results (CI 95%) 90% CI if ♣ Sig. ($p \leq 0.05$) if * Sig. ($p \leq 0.01$) if**	Comments
Walrath and Fraumeni, 1983	Embalmers (New York state) According to a NIOSH study, employees were exposed to more than 3 ppm during embalming when ventilation was poor, and between 0.2 and 0.9 ppm when ventilation was adequate. A survey of 6 funeral homes revealed levels between 0.1 and 5.3 ppm, with average levels between 0.25 and 1.4 ppm.	- Oral cavity and pharyngeal (8) Embalmers (7) Embalmers and funeral dir. (1) - Nasopharyngeal (0) - Sinus and nasal cavities (0) - Laryngeal (2)	PMR: 113 PMR: 201 PMR: 28 0.5 expected 3.4 expected	• Lacks power: Few cases, results not significant. • Possible misclassification of exposure. Little information about exact levels. Measurements taken after. No data on time and frequency of exposure. • Cancer primarily identified from death certificates. • With the PMR risk measurement, the relative frequency of other causes of death can modify the proportional mortality of the cancer of interest. • Possible effect of healthy occupation given that the comparison was made with the general population. Workers were usually healthier than the general population. • Possibility that another uncontrolled factor contributed to the observed risk. The authors only controlled for age, race and time. They did not control for several possible confounding factors (cigarette and alcohol use, nutrition, socio-economic class). According to the authors, the embalmers were also exposed to skin moisturizers, antiseptic solutions, dyes and deodorants, among other substances. However, they were not exposed to wood dust.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤ 0.05) if * Sig. (p≤ 0.01) if **	Comments
Walrath and Fraumeni, 1984	Embalmers (State of California) According to a NIOSH study, employees are exposed to over 3 ppm during an embalming, when ventilation is low and between 0.2 and 0.9 ppm when ventilation is sufficient. A survey of 6 funeral homes revealed levels of between 0.1 and 5.3 ppm, with mean levels of between 0.25 and 1.4 ppm.	Oral cavity and pharyngeal (8) Exp. < 20 yrs (5) Exp. ≥ 20 yrs (3) Nasopharyngeal (0) Sinus and nasal cavities (0) Laryngeal (2)	PMR: 131 PMR: 166 PMR: 97 0.6 expected 2.6 expected	• Lacks power: Few cases, results not significant. • Improper classification of exposure possible. Little information on specific levels. Measures were performed afterwards. No information on duration or frequency of exposure. • Cancer identified principally from death certificates. • Using the PMR risk measure, the relative frequency of other causes of death can modify the proportionate mortality of the cancer of interest. • Health effect of employment is possible, given that the comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled only for age, race and time period. They did not control many additional confounding factors (cigarette and alcohol consumption, nutritional status, social class). Among other things, according to the authors, embalmers were also exposed to coloring agents and modifiers, anticoagulants, surfactants, deodorants and vehicles. They were not, however, exposed to fine sawdust.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Blair *et al.*, 1986	Male industrial workers in 10 American industries 11% considered non-exposed, 12% exposed to less than 0.1 ppm, 34% exposed to 0.1-0.5 ppm, 40% exposed to 0.5-2 ppm and 4% exposed at levels higher than 2 ppm.	- Oral cavity and pharynx (18 exp.) 0 ppm-yr (2) ≤ 0.5 ppm-yr (10) 0.5-5.5 ppm-yr (5) ≥ 5.5 ppm-yr (4) - Larynx (12 exp.) 0 ppm-yr (3) ≤ 0.5 ppm-yr (6) 0.5-5.5 ppm-yr (6) ≥ 5.5 ppm-yr (1) - Nasopharynx (6) 0 ppm-yr (1) ≤ 0.5 ppm-yr (2) 0.5-5.5 ppm-yr (2) ≥ 5.5 ppm-yr (2) - Oropharynx ≤0.5 ppm-yr (4) 0.5-5.5 ppm-yr (1) - Hypopharynx 0 ppm-yr (1) ≤ 0.5 ppm-yr (1) - Sinus and nasal cavities (2)	SMR: 96 (57-152) SMR: 89 (11-323) SMR: 132 (63-242) SMR: 56 (18-131) SMR: 73 (20-186) SMR: 142 (73-248) SMR: 292 (60-853) SMR: 180 (66-391) SMR: 147 (54-320) SMR: 39 (1-218) SMR: 270* SMR: 530 SMR: 271 SMR: 256 SMR: 433 SMR: 443 * SMR: 95 SMR: 594 SMR: 172 2.2 expected	• Lacks power: Few cases, results not significant. • Improper classification of exposure possible. A few directly measured data available. The quality and quantity of measurements varied between institutions. Facility hygienists revised the classifications. Afterward, direct measurements were taken to validate historic data. • Calculated cumulative exposure in ppm/year not very useful. Severity of injury appears more closely associated with formaldehyde concentrations present in air rather than cumulative exposure. • Cancer identified principally from death certificates. Tests were performed for practically all possible causes of death, many of which were not biologically plausible. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled only for age, gender, race and time period. They stratified for social class for one of the analyses. They did not control many additional confounding factors (fine sawdust, cigarette and alcohol consumption, nutritional status). • No significant dose-response relationship was observed. An opposite relation and risk were also often observed in non-exposed people.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Blair *et al.*, 1987	Male industrial workers in 10 American industries Re-analysis of Blair 1986 but controlling for particles.	- Nasopharynx (also exposed to particles) 0 ppm-yr (0) ≤ 0.5 ppm-yr (1) 0.5-5.5 ppm-yr (2) ≥ 5.5 ppm-yr (2) (not exposed to particles) 0 ppm-yr (1) ≤ 0.5 ppm-yr (1) 0.5-5.5 ppm-yr (0) ≥ 5.5 ppm-yr (0) - Oropharynx (also exposed to particles) 0 ppm-yr (0) ≤ 0.5 ppm-yr (3) 0.5-5.5 ppm-yr (0) ≥ 5.5 ppm-yr (0) (not exposed to particles) 0 ppm-yr (0) ≤ 0.5 ppm-yr (1) 0.5-5.5 ppm-yr (1) ≥ 5.5 ppm-yr (0)	 0 expected SMR: 192 SMR: 403 SMR: 746 SMR: 532 SMR: 416 0.3 expected 0.2 expected 0 expected SMR: 457 0.7 expected 0.4 expected 0.2 expected SMR: 354 SMR: 264 0.3 expected	• Lacks power: Few cases, results not significant. • Improper classification of exposure possible. A few directly measured data available. The quality and quantity of measurements varied between institutions. Facility hygienists revised the classifications. Afterward, direct measurements were taken to validate historic data. • Calculated cumulative exposure in ppm/year not very useful. Severity of injury appears more closely associated with formaldehyde concentrations present in air rather than cumulative exposure. • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled only for age, gender, race and time period. They stratified for exposure and lack of exposure to particles. They did not control many additional confounding factors (cigarette and alcohol consumption, nutritional status, social class). • No significant dose-response relationship was observed. Increased risk (not significant) was found as a function of cumulative exposure to formaldehyde in the presence of particles. A risk (not significant) was also found in persons not exposed to formaldehyde and to particles.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Collins et al., 1988	Male industrial workers in 10 American industries Re-analysis of Blair 1986 with 5 years more follow-up Stratification for particle exposure. Analysis by duration of employment and by facility.	- Nasopharynx (particles present) (5) 0 ppm-yr (2) ≤ 0.5 ppm-yr (2) 0.5-5.5 ppm-yr (1) ≥ 5.5 ppm-yr (2) (particles present, facility 1) (4) 0 ppm-yr (0) ≤ 0.5 ppm-yr (2) 0.5-5.5 ppm-yr (1) ≥ 5.5 ppm-yr (1) (particles present, facilities 2-10) (4) Employees for less than 1 year (3) Employees for more than 1 year (3)	SMR: 388 * SMR: 215 SMR: 343 SMR: 216 SMR: 826 * SMR: 1026 ** 0.5 expected SMR: 1475 * SMR: 624 SMR: 1095 SMR: 111 SMR: 517 * SMR: 218	• Lacks power: Few cases, results not significant. • Improper classification of exposure possible. A few directly measured data available. The quality and quantity of measurements varied between institutions. Facility hygienists revised the classifications. Afterward, direct measurements were taken to validate historic data. • Calculated cumulative exposure in ppm/year not very useful. Severity of injury appears more closely associated with formaldehyde concentrations present in air rather than cumulative exposure. • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age, gender, race and time period. They stratified for exposure to particles. They did not control many additional confounding factors (cigarette and alcohol consumption, nutritional status, social class). • No significant dose-response relationship was observed. Particularly elevated risk was found for employees of facility 1 but not in employees of other facilities (2-10). Formaldehyde is therefore probably not the only issue. In addition, significant risk was observed in those workers who had worked for less than one year but not in long-term employees. Short-term employees are normally excluded from the analysis because their exposure is often negligible with respect to past and future exposure to other substances.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Stayner *et al.*, 1988	Clothing industry workers in 3 American facilities Recent continuous measurements show that employees are exposed to low constant levels (mean: 0.15 ppm) during their shifts. Prior exposures, though undocumented, probably higher, due to recent system improvements.	- Oral cavity and pharynx (6) - Oral cavity (4) - Pharynx (2) - Oral cavity, exposure duration ≥ 10 yrs (3) - Nasopharynx (0) - Sinus and nasal cavities (0)	SMR: 155 (68-307) ♣ SMR: 343 (118-786) ♣* SMR: 113 (20-359) ♣ SMR: 757 **	• Lacks power: Few cases, results not significant. Confidence intervals of 90% rather than 95%. • Improper classification of exposure possible. Lack of direct historic measurements, only recent measurements. Rather low exposure. • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. They did not control many additional confounding factors (cigarette and alcohol consumption, nutritional status, social class). They sampled to confirm absence of phenol, organic cleaning solvents and deleterious dusts. According to the authors, there has been no known workplace exposure of these workers to a carcinogenic agent.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Hayes et al., 1990	American funeral services workers. Based on a few measurements taken for the study, workers are exposed to 3.99 ppm during embalming, when ventilation is low, and to 0.98 ppm when ventilation is high. Studies in embalmers assess mean exposure at 1 ppm or less.	- Oral cavity and pharynx (30) - Nasopharynx (4) - Sinus and nasal cavities (0) - Larynx (7)	PMR: 120 (81-171) PMR: 216 (59-554) 1.7 cases expected PMR: 64 (26-133)	• Lacks power: few cases, results not significant. • Improper classification of exposure possible. Little information on precise levels. Measurements taken afterward. No information on duration and frequency of exposure. • Cancer identified principally from death certificates. • Using the PMR risk measure, the relative frequency of other causes of death can modify the proportionate mortality of the cancer of interest. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age, gender, race and time period. They did not control many additional confounding factors (cigarette and alcohol consumption, nutritional status, social class). Among other things, according to the authors, embalmers were also exposed to drying and hardening powders, to dusts, phenol, methyl alcohol, glutaraldehyde, tissue and biological material fixatives. In the past, they were exposed to mercury, arsenic and zinc.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Gardner *et al.*, 1993	Workers in 6 British chemical industries. Exposure categories: less than 0.1 ppm, 0.1-0.5 ppm, 0.6-2 ppm and over 2 ppm. 35% of the cohort hired before 1965 and 21% of the cohort hired after 1964 were exposed to over 2 ppm.	- Nasal cavity before 1965 (1) after 1964 (0) - Pharynx before 1965 (7) after 1964 (0) - Larynx before 1965 (8) after 1964 (0) - Nasopharynx (0)	 SMR: 70 (2-390) 0.3 expected SMR: 147 (59-303) 1.1 expected SMR: 118 (51-232) 1.3 expected 1.3 expected	• Lacks power: few cases, results not significant. • Improper classification of exposure possible. Classification based on employment titles for each worker before 1982. Lack of direct measurements before 1970. Assessment also based on acute symptoms of irritation reported by workers. • Elevated proportion of workers exposed to over 2 ppm. However, can one really have confidence in the 35% and 21% values, and in the 2 ppm value? • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age, gender, race and time period. They did not control many additional confounding factors (fine sawdust, cigarette and alcohol consumption, nutritional status, social class). Among other things, according to the authors, the workers may also have been exposed to asbestos, Scandinavian wood fibre, epichlorohydrin, triphosphate (2, 3-dibromopropyl) and chromium pigments.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Hansen and Olsen, 1995	Male industrial workers in Denmark. Companies using or producing more than 1 kg of formaldehyde per employee per year. Employees stratified into two exposure categories: low (white collar) and above baseline levels (blue collar). No precise exposure levels available.	- Oral cavity and pharynx (23) - Nasopharynx (4) - Nasal cavities (13) - Larynx (32) - Nasal cavities (low exp.) (1) - Nasal cavities (higher exp. without fine sawdust exp.) (9) - Nasal cavities (higher exp. with fine sawdust exp.) (2)	SPIR: 1.1 (0.7-1.7) SPIR: 1.3 (0.3-3.2) SPIR: 2.3 (1.3-4.0)* SPIR: 0.9 (0.6-1.2) SPIR: 0.8 (0.02-4.4) SPIR: 3.0 (1.4-5.7)* SPIR: 5.0 (0.5-13.4)	• Lacks power: few cases, results not significant. • Improper classification of exposure possible. No precise information on levels of exposure. Exposure assessed according to annual production and type of employment available in from Danish pension supplementary funds (only since 1964). Exposure based on the longest period of employment per employee. Only non-differential misclassification. • Cancer identified in the cancer registry of Denmark. • Using the SPIR risk measure, the relative frequency of other causes of death can modify the proportionate mortality of the cancer of interest. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age and time period. They did not control many additional confounding factors (fine sawdust, cigarette and alcohol consumption, nutritional status, social class).

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Andjelkovich *et al.*, 1995	Workers at an American foundry. Highest levels of exposure are estimated at 2.6 ppm before 1978, 1.8 ppm between 1978-83 and 1.2 ppm since 1984. Exposure classified according to 4 categories: High (≈1.5 ppm), Mean (≈0.55 ppm), Low (≈0.05 ppm) and Nil.	- Oral cavity and pharynx FM exposures (6) non-exposed (5) exposed vs non-exp. exposed vs non-exp. high exposures (3rd and 4th quartile) vs non-exp. - Larynx HM exposures (2) non-exposed (1) exposed vs non-exp. - Sinus and nasal cavities (0) - Nasopharynx exposed (0) non-exposed (1)	 SMR: 131 (48-286) SMR: 169 (54-395) Ratio directly adjusted: 70 RR: 0.59 (0.14-2.93) RR: 1.16 (0.20-6.51) SMR: 98 (11-353) SMR: 70 (1-391) Ratio directly adjusted: 150	• Lacks power: few cases, results not significant. • Improper classification of exposure possible. In order to determine exposure levels, the following data were used: sampling measurements, technical information regarding the facility, knowledge of foundry and welding procedures, job description and tasks performed. Then each job was assigned to an exposure category. • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. The authors also compared the exposed versus non-exposed workers, which eliminates the health effect of work for those measures. • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age, gender, race and time period. They also obtained information on cigarette use for 65% of the exposed and 55% of non-exposed workers. They did not control many additional confounding factors (fine sawdust, alcohol consumption, nutritional status, social class). According to the authors, it was not possible to adequately assess the role that silica may have played. Among the 6 oral cavity and pharynx cancer, 5 were smokers and information was lacking regarding the 6th case.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) CI 90% if ♣ Sig. (p≤0.05) if * Sig. (p≤0.01) if **	Comments
Marsh *et al.*, 1996	Male industrial workers in an American industry (Blair 1986 facility 1) Sporadic measurements between 1965 and 1987 for 42 job titles. The highest TWA (mean 8 hour exp.) was 2.8 ppm in 1972. Only 12 measures higher than TWA of 1 ppm. In total, 9.5% of short term employees and 32.3% of long term employees were exposed to levels higher than 0.7 ppm.	- Oral cavity (6) - Oral cavity and pharynx Short term (10) Long term (5) Short term and hired between 1947-56 (9) Long term and hired between 1947-56 (3) - Oropharynx (2) - Nasopharynx (4) Short term (2) Long term (2) Short term and hired between 1947-56 (2) Long term and hired between 1947-56 (2) - Laryngopharynx (1) - Sinus and nasal cavities (2) - Larynx (6)	SMR: 131 SMR: 164 SMR: 91 SMR: 229 * SMR: 102 SMR: 184 SMR: 533 * SMR: 515 SMR: 596 SMR: 768 SMR: 1049 * SMR: 141 SMR: 381 SMR: 147	• Lacks power: few cases, results not significant. • Improper classification of exposure possible. Estimation based on: a few sporadic direct measurement data available, job descriptions and oral descriptions of jobs and tasks by staff of the facility and industrial hygienist. • Cancer identified principally from death certificates. • Health effect of employment is possible, given that comparison is being made with general population. Employed persons are normally healthier than the general population. Three different populations were used in comparison (US, Connecticut and county). • Possibility that another uncontrolled factor may have contributed to the observed risk. Note that the authors controlled for age, gender, race and time period. They did not control many additional confounding factors (fine sawdust, cigarette and alcohol consumption, nutritional status, social class). • Short term employees were often excluded from the analysis because their exposure is often negligible with respect to past and future exposure to other substances. • All nasopharyngeal cancer and the majority of oral cavity and pharyngeal cancers were found in employees hired between 1947 and 1956. Formaldehyde is probably not the only issue. It should be noted that 45% of long-term employees hired between 1947-56 were exposed to levels greater than 0.7%, which is a higher proportion compared to employees hired during any other period.

Analysis of Meta Analysis Type Studies

Three meta analysis type studies were chosen and analyzed. A summary of each study and corresponding comments are provided in Table 3.

Table 3: Presentation and Analysis of Meta Analysis Type Studies
RR: relative risk, mRR: meta relative risk, CI: confidence interval, Sig.: significant

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) Sig. ($p \leq 0.05$) if *	Comments
Blair *et al.*, 1990	Meta analysis of over 30 case-control type studies and cohort studies pertaining to industrial workers and professionals in 8 different nations. Professionals: mean TWA exposure over 8 hours from 0.3 to 1.3 ppm reported during embalming. Recent assessments found TWA of 0.8 to 2.9 ppm. A TWA of 0.02 to 5.87 ppm was reported for anatomists. Industrial workers: Levels vary among studies and were generally reported. Over 5.5 ppm-year is considered a high exposure level. Less than 5.5 ppm-year is therefore considered a low exposure level.	- Oral cavity and pharynx Professionals (51) Industrial workers (92) - Nasopharynx Professionals (4) Industrial workers (31) Low level and duration (30) High level and duration (13) - Sinus and nasal cavities Professionals (1) Industrial workers (60) Low level and duration (38) High level and duration (30)	 RR: 1.0 RR: 1.0 RR: 2.2 RR: 1.2 RR: 1.1 RR: 2.1* RR: 0.4 RR: 1.1 RR: 0.8 RR: 1.1	• Power acceptable. Few significant results but this is not due to lack of power, but rather the lack of risk. • Improper classification of exposure possible. Assessment of exposure varies between studies. If the classification was biased in most studies, this will also be true of the meta analysis. • Possibility that another uncontrolled factor may have contributed to the observed risk. Few factors were controlled for. The controlled factors varied between studies. • Same weaknesses as studies taken separately. The results of a larger study may have a great influence on the results of the combined studies. • A significant dose-response relationship is observed for nasopharyngeal cancer.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) Sig. (p≤0.05) if *	Comments
Partanen, 1993	Meta analysis of over 30 case-control type studies and cohort studies pertaining to industrial workers and professionals. Same studies as used by Blair 1990 with a few updates.	- Sinus and nasal cavities Exposure (93) Low to med. exp. (33) High exp. (36) - Nasopharynx Exposure (36) Low to med. exp. (23) High exp. (11) - Other oral cavity sites and pharynx Exposure (69) Low to med. exp. (52) High exp. (23)	 RR: 1.19 (0.96-1.46) RR: 1.09 (0.74-1.55) RR: 1.75 (1.21-2.43)* RR: 1.74 (1.21-2.41)* RR: 1.44 (0.91-2.16) RR: 2.59 (1.29-5.36)* RR: 1.22 (0.95-1.54) RR: 1.08 (0.80-1.42) RR: 1.16 (0.74-1.75)	• Power acceptable. • Improper classification of exposure possible. Assessment of exposure varies between studies. If the classification was biased in most studies, this will also be true of the meta analysis. • Possibility that another uncontrolled factor may have contributed to the observed risk. Few factors were controlled. The controlled factors varied between studies. • RR calculated using Poisson regression analysis. Authors also used Log-Gauss (similar results). • Same weaknesses as studies taken separately. The results of a larger study may have a great influence on the results of the combined studies. • Significant risk observed for nasopharynx, sinus and nasal cavities among highly exposed workers.

Study	Population and exposure levels	Types of cancer studied (number of cases)	Results (CI 95%) Sig. (p≤0.05) if *	Comments
Collins *et al.*, 1997	Meta analysis of 47 case-control type studies and cohort studies pertaining to industrial workers and professionals. Same studies as used by Blair 1990 with a few updates. <u>Cohort type studies:</u> Industrial workers working in production and manufacture of formaldehyde with TWA of between 0.1 and 3.4 ppm from 1977 to 1988. For those in the clothing industry, TWA was between 0.1 and 1.9 ppm. Foundry workers had a TWA of between 0.3 and 2.8 ppm while embalmers had a TWA between 0.3 and 2.6 ppm. Finally, medical specialists had a TWA of between 0.1 and 1.1 ppm. <u>Case-control type studies</u>: Assessment of exposure is less certain for this type of study. The authors reassessed exposure and did not assess any job that was likely to have a mean concentration of over 2 ppm. 4 of 26 jobs had mean exposures of between 1 and 2 ppm. All other jobs had lower exposure and low prevalence. In general, exposure levels were considerably lower in the case-control type studies than in the cohort type studies.	- Sinus and nasal cavities all types (939) cohort (3) case-control (933) United States (351) (low fine sawdust) Europe (582) (fine sawdust) - Nasopharynx all types (455) cohort (10) case-control (445)	 MRR: 1.0 (1.0-1.1) MRR: 0.3 (0.1-0.9)* MRR: 1.8 (1.4-2.3)* MRR: 1.0 (0.7-1.5) MRR: 2.9 (2.2-4.0)* MRR: 1.3 (1.2-1.5)* MRR: 1.6 (0.8-3.0) MRR: 1.3 (0.9-2.1)	• Power interesting. • Improper classification of exposure possible. Assessment of exposure varies between studies. If the classification was biased in most studies, this will also be true of the meta analysis. • Possibility that another uncontrolled factor may have contributed to the observed risk. Few factors were controlled for. The controlled factors varied between studies. • Same weaknesses as studies taken separately. The results of a larger study may have a great influence on the results of the combined studies. • The authors stratified by type of study which was particularly interesting for the sinus and nasal cavity cancer, where two opposing conclusions were found for the 2 types of studies. Both conclusions were also significant. Note that risk was observed for the case-control studies where exposure was considered the lowest. • There was also a considerable difference between the studies conducted in the United States and those in Europe, possibly due to the fine sawdust effect. • Significant risk observed for nasopharynx cancer when both types of study are combined. The results are similar for both types of studies.

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