CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name: FORMALDEHYDE … %

EC Number: 200-001-8

CAS Number: 50-00-0

Index Number: 605-001-00-5

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Part A.

List of abbreviations

AML: acute myeloid leukaemia
ALL: acute lymphocytic leukaemia
BAL: Broncho-alveolar lavage
BrdUrd: 5-bromodeoxyuirdine
CA : chromosomal aberration
CI: confidence interval
CML: chronic myeloid leukaemia
CLL: chronic lymphocytic leukaemia
CPA: cyclophosphamide
DPX : DNA-protein crosslink
dAdo: deoxyadenosine
FA: formaldehyde
HNEC: Human Nasal Epithelial Cells
IP: intra-peritoneal
LM: lateral meatus
ML: myeloid leukaemia
MN: micronucleus
M:PM: medial and posterior meatus
MRR: meta-relative risk
NALT: nasal-associated lymphoid tissue
NHL: Non-Hodgkin lymphoma
NOAEL: No observable adverse effect level
4-NOQ: 4-nitroquinoline 1-oxide
NPC: nasopharynx carcinoma
OR: odd ratio
PMR: proportionate mortality ratio
RCP: regenerative cell proliferation
ROS: reactive oxygen species
RR: relative risk
SCE: sister chromatid exchange
SCL: specific concentration limit
SIR: standardised incidence ratio
SMR: standardised mortality ratio
SPICR: standardised proportionate incidence cancer ratios
TWA: time-weighted average concentration

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

The present CLH report deals with the toxicological properties of formaldehyde, a gaseous substance at room temperature.

However, formaldehyde is used and commercialised as aqueous solutions that forms gaseous formaldehyde when used.

The existing harmonised entry and present proposal of revision is entitled "formaldehyde … %" and refers to the aqueous solution of formaldehyde.

Table 1: Substance identity

Substance name:	***Formaldehyde***
EC number:	***200-001-8***
CAS number:	***50-00-0***
Annex VI Index number:	***605-001-00-5***
Degree of purity:	***100% as gas***
Impurities:	***None as gas***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Acute Tox. 3 – H331* Acute Tox. 3 – H311* Acute Tox. 3 – H301* Skin Corr. 1B – H314 (SCL: Skin Corr 1B ≥25%, 5%≤ Skin Irrit 2/Eye Irrit 2<25%, STOT SE 3 – H335 ≥5%)	T; R23/24/25 (SCL: T ≥25%, 5%≤Xn<25%) C; R34 (SCL: C ≥25%, 5%≤Xi; R36/37/38<25%)

	Skin Sens. 1 – H317(SCL of 0.2%) Carc. 2 – H351 Notes B, D (see content below)	R43 (SCL of 0.2%) Carc. Cat. 3; R40 Notes B, D
Current proposal for consideration by RAC	[STOT SE 3 – H335][#] Muta 2 – H341 Carc. 1A – H35	Muta cat. 3 ; R68 Carc. Cat. 1; R45
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 3 – H331* Acute Tox. 3 – H311* Acute Tox. 3 – H301* Skin Corr. 1B – H314 (SCL: Skin Corr 1B ≥25%, 5%≤ Skin Irrit 2/Eye Irrit 2<25%, STOT SE 3- H335 ≥5%) Skin Sens. 1 – H317(SCL of 0.2%) [STOT SE 3 – H335][#] Muta 2 – H341 Carc. 1A – H350 Notes B, D (see content below)	T; R23/24/25 (SCL: T ≥25%, 5%≤Xn<25%) C; R34 (SCL: C ≥25%, 5%≤Xi; R36/37/38<25%) R43 (SCL of 0.2%) Muta cat. 3; R68 Carc. Cat. 1; R45 Notes B, D

* minimum classification

[#]It is noted that STOT SE 3- H335 appears in the SCL in the Table 3.2 of Annex VI whereas it doesn't appear as a classification of formaldehyde *per se*. It is assumed that its inclusion in the SCL results from the automatic translation of R37 in Directive 67/548, in which R37 can be derived from the corrosive classification. However it is not our understanding of the CLP criteria that STOT SE 3; H335 can be derived from a Skin Corr 1B classification. To correct this inconsistency between the CLP classification and the CLP SCL, STOT SE 3; H335 should be added in the classification of formaldehyde. No scientific discussion is expected on this comment that is purely based on regulatory considerations and no information is displayed in Part B section 4.4 on this endpoint. STOT SE3 is therefore not proposed for consideration by the RAC. Besides, it is noted that full review of the classification of formaldehyde will be performed in the context of its evaluation as a biocidal active substance.

Note B: Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different classification and labelling since the hazards vary at different concentrations. In Part 3 entries with Note B have a general designation of the following type: 'nitric acid … %'. In this case the supplier must state the percentage concentration of the solution on the label. Unless otherwise stated, it is assumed that the percentage concentration is calculated on a weight/weight basis.

Note D: Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in Part 3. However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the supplier must state on the label the name of the substance followed by the words 'non-stabilised'.

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not evaluated
2.2.	Flammable gases	None		None	Not evaluated
2.3.	Flammable aerosols	None		None	Not evaluated
2.4.	Oxidising gases	None		None	Not evaluated
2.5.	Gases under pressure	None		None	Not evaluated
2.6.	Flammable liquids	None		None	Not evaluated
2.7.	Flammable solids	None		None	Not evaluated
2.8.	Self-reactive substances and mixtures	None		None	Not evaluated
2.9.	Pyrophoric liquids	None		None	Not evaluated
2.10.	Pyrophoric solids	None		None	Not evaluated
2.11.	Self-heating substances and mixtures	None		None	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not evaluated
2.13.	Oxidising liquids	None		None	Not evaluated
2.14.	Oxidising solids	None		None	Not evaluated
2.15.	Organic peroxides	None		None	Not evaluated
2.16.	Substance and mixtures corrosive to metals	None		None	Not evaluated
3.1.	Acute toxicity - oral	None		Acute 3	
	Acute toxicity - dermal	None		Acute 3	
	Acute toxicity - inhalation	None		Acute 3	
3.2.	Skin corrosion / irritation	None		Skin Corr 1B≥25%	
3.3.	Serious eye damage / eye irritation	None		5% ≤ Eye Irrit 2 <25%	
3.4.	Respiratory sensitisation	None		None	Not evaluated
3.4.	Skin sensitisation	None		Skin Sens. 1 ≥0.2%	Not evaluated
3.5.	Germ cell mutagenicity	Muta 2	None	None	
3.6.	Carcinogenicity	Carc 1A	None	Carc 2	
3.7.	Reproductive toxicity	None		None	Not evaluated
3.8.	Specific target organ toxicity –single exposure	[STOT SE 3]*	[5%]*	None	
3.9.	Specific target organ toxicity	None		None	Not evaluated

	– repeated exposure				
3.10.	Aspiration hazard	None		None	Not evaluated
4.1.	Hazardous to the aquatic environment	None		None	Not evaluated
5.1.	Hazardous to the ozone layer	None		None	Not evaluated

1) Including specific concentration limits (SCLs) and M-factors
2) Data lacking, inconclusive, or conclusive but not sufficient for classification
* see footnote of table 2.

Labelling: Signal word: Dgr
Pictogram codes: GHS06, GHS08, GHS05
Hazard statements: H350, H341, [H335]*, H331, H311, H301, H314, H317
Precautionary statements: not harmonised

Proposed notes assigned to an entry: B, D

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification** [1]	**Reason for no classification** [2]
Explosiveness	None		None	Not evaluated
Oxidising properties	None		None	Not evaluated
Flammability	None		None	Not evaluated
Other physico-chemical properties *[Add rows when relevant]*	None		None	Not evaluated
Thermal stability	None		None	Not evaluated
Acute toxicity	None		T; R23/24/25≥25 %	
Acute toxicity – irreversible damage after single exposure	None		None	Not evaluated
Repeated dose toxicity	None		None	Not evaluated
Irritation / Corrosion	None		C; R34≥25 % 5 % ≤ Xi; R36/37/38 < 25 %	
Sensitisation	None		R43≥ 0,2 %	
Carcinogenicity	Carc. Cat. 1	None	Carc. Cat. 3	
Mutagenicity – Genetic toxicity	Muta Cat. 3	None	None	
Toxicity to reproduction – fertility	None		None	Not evaluated
Toxicity to reproduction – development	None		None	Not evaluated
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Not evaluated
Environment	None		None	Not evaluated

[1] Including SCLs
[2] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: T
R-phrases: R23/24/25- R34 – R43 – R45 – R68
S-phrases: S1/2- S45- S53

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

The classification of aqueous solutions of formaldehyde (…%) is harmonised in Annex VI of CLP under the index number 605-001-00-5 as follows:

Carc. Cat. 3; R40

T; R23/24/25 (SCL: T ≥25%, 5%≤Xn<25%)

C; R34 (SCL: C ≥25%, 5%≤Xi; R36/37/38<25%)

R43 (SCL of 0.2%)

Note B, D

Classification of formaldehyde was inserted in the 1st ATP (1976) of Annexe I of Directive 67/548/EEC. Carcinogenicity classification was inserted in the 8th ATP in 1987 and has not been modified since then. The last update of formaldehyde classification was included in the 22nd ATP of Directive 67/548/EEC (1996) and focused on the adoption of SCL for skin irritation.

It is not known whether discussions on the carcinogenicity and mutagenicity of formaldehyde have taken place since the first insertion of carcinogenic classification in Annexe I. However, no discussion on these endpoints has taken place at least from the 22nd ATP to our knowledge.

A classification proposal was submitted by the French CA at the TC C&L and was presented at the TC C&L of November 2005. No discussion took place as several Members States were not ready for discussion. The substance was removed from the agenda of TC C&L of March 2006 and October 2006, as it was decided that the update of the NCI cohort and national positions of the MS should be awaited. No further discussion took place at the TC C&L.

2.2 Short summary of the scientific justification for the CLH proposal

The International Agency for Research on Cancer (IARC) has evaluated the carcinogenity of formaldehyde several times. In 2006, IARC concluded that formaldehyde is a known human carcinogen (group 1) on the basis of induction of nasopharyngeal cancers (IARC 2006). It was reaffirmed in its re-evaluation of 2009 and extended to the induction of leukaemia and particularly myeloid leukaemia (Baan 2010).

A large amount of new relevant data on carcinogenicity and mutagenicity of formaldehyde has been published in the past 15 years that has not been evaluated by the TC C&L (see history of formaldehyde classification in 2.1) and the French Competent Authorities considers that the classification for carcinogenicity and mutagenicity needs to be revised on the basis of the new studies available. Several reviews of the toxicological properties of formaldehyde have also been published by international or national organisations as discussed in section 6 of this report.

On mutagenicity, positive evidence are available i*n vivo* at the site of contact in somatic cells. They consist in induction of chromosomal aberrations in rats by inhalation at high dose (Dallas 1992) and of micronuclei in rats in the gastrointestinal tract by oral route (Migliore 1989). These positive data are further supported by *in vitro* positive results in numerous genotoxicity and mutagenicity tests, *in vivo* induction of DNA adducts and DNA-protein crosslinks (DPX) at the site of contact and indications of consistent increases in micronuclei frequency in humans at the site of contact. Based on induction of genotoxic and mutagenic effects of formaldehyde on somatic cells at the site of contact, **classification in Category 2 is warranted**.

On carcinogenicity, experimental data clearly provide evidence of a carcinogenic effect at the site of contact in rats by inhalation. Although this finding is restricted to a single species (rat), consistent results were obtained from several independent studies and in both females and males. Tumours consists in both benign and malignant tumours but were induced at a single site (nasal cavity). Data investigating the mode of action support the existence of a threshold type mode of action for its carcinogenic properties based on the cytotoxic effect of formaldehyde. Genotoxicity is also expected to play a role above this threshold. **Overall the level of experimental evidence is judged as sufficient evidence in agreement with induction of tumours (b) [in] two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.**

<u>At the site of contact</u>, positive epidemiological evidence of association from both cohort studies and case-control studies were identified for nasopharynx. Results were statistically significant and supported by trends with exposure in both types of studies. However, the existence of a grouping of cases in plant 1 of the National Cancer Institute (NCI) cohort raises a doubt on potential cofounder and lowers the level of evidence. But the grouping of cases but it can also be explained by the largest number of subjects exposed to high peaks in this specific plant. Several factors however support the existence of a carcinogenic potential of formaldehyde at the site of contact:

- Induction of tumours in the nasal cavity in rats with a proposed mode of action based on chronic irritation of the respiratory tract and local genotoxicity at doses inducing an increased proliferation
- Indication of local genotoxicity in exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells in several studies
- Human sensitivity to FA-induced irritation, with irritation of the eye and of the nose/throat being consistently reported after exposure to formaldehyde (IARC 2006).

No species-specific mechanism is evident and human data denote human sensitivity to FA effects (genotoxicity and irritation). The mode of action of carcinogenicity in the rat nasal cavity is therefore considered relevant to humans, as reviewed in the context of the IPCS framework (McGregor 2007).

The induction of nasopharyngeal carcinomas in human exposed to formaldehyde is therefore strongly plausible.

The biological plausibility of the induction of nasopharyngeal carcinomas in humans exposed to formaldehyde highly supports the consistent epidemiological evidence obtained from the NCI cohort and from several case-control studies. It is considered that the doubt of a potential cofounder is raised by the grouping of cases in the plant 1 of the NCI cohort. But considering the overall database and more specifically the fact that the grouping of cases in plant 1 can also be explained by the largest number of subjects exposed to high peaks in this specific plant, correlation of NPC with the level of peak exposure to formaldehyde, the evidence provided by case-control studies and the biological plausibility, the doubt that the observed induction of NPC may be due to confounder can be ruled out *with reasonable confidence*.

Altogether, the data support a causal relationship between formaldehyde exposure and induction of NPC and corresponds to a sufficient evidence of carcinogenicity in humans.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

The classification of formaldehyde is harmonised in Annex VI of CLP under the index number 605-001-00-5 as follows:

Table 3.1 (CLP)
Acute Tox. 3 – H331* Acute Tox. 3 – H311* Acute Tox. 3 – H301* Skin Corr. 1B – H314 (SCL: Skin Corr 1B ≥25%, 5%≤ Skin Irrit 2/Eye Irrit 2<25%, STOT SE 3 – H335 ≥5%) Skin Sens. 1 – H317(SCL of 0.2%) Carc. 2 – H351 Notes B, D * minimum classification

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

The classification of formaldehyde is harmonised in Annex VI of CLP under the index number 605-001-00-5 as follows:

Table 3.2 (67/548/EEC)
T; R23/24/25 (SCL: T ≥25%, 5%≤Xn<25%) C; R34 (SCL: C ≥25%, 5%≤Xi; R36/37/38<25%) R43 (SCL of 0.2%) Carc. Cat. 3; R40 Notes B, D

2.4 Current self-classification and labelling

Not relevant

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Formaldehyde has a harmonised classification and labelling (as aqueous solution) in Annex VI of CLP that includes classification for carcinogenicity.

A large amount of new relevant data on carcinogenicity and on mutagenicity of formaldehyde has been published in the past 15 years that has not been evaluated by the TC C&L (see history of formaldehyde classification in 2.1).

The French Competent Authorities considers that the classification for carcinogenicity and mutagenicity needs to be revised on the basis of the new studies available.

Carcinogenicity and mutagenicity as other CMR properties justifies a harmonised classification and labelling according to article 36 of CLP.

Regulatory considerations are added on STOT SE3 –H335 (see footnote of table 2) but this endpoint is not proposed for consideration by the RAC. Besides, it is noted that full review of the classification of formaldehyde will be performed in the context of its evaluation as a biocidal active substance.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

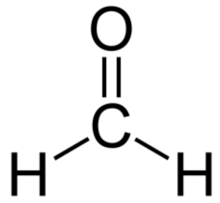
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	200-001-8
EC name:	Formaldehyde Synonyms: formaldehyde gas, formaldehyde solution, methanal, formic aldehyde, methylene oxide, oxymethylene, methylaldehyde, oxomethane, formol, formalin, formalith, méthylaldehyde, morbicid, oxomethane, paraform.
CAS number (EC inventory):	50-00-0
CAS number:	50-00-0
CAS name:	Formaldehyde
IUPAC name:	Formaldehyde
CLP Annex VI Index number:	605-001-00-5
Molecular formula:	CH_2O
Molecular weight range:	30.026 g/mol

Structural formula:



1.2 Composition of the substance

The information presented in this section refers to aqueous solutions of formaldehyde that are the object of the current proposal of classification revision.

The specified purity, additives and impurities refer to 49-49.3% solutions of formaldehyde and are based on data available in the litterature (OECD 2002).

Information based on the registration dossiers of formaldehyde is given in the confidential Appendix I to the present report (see separate file).

Purity of gaseous formaldehyde is assumed to be 100%.

Table 6: Constituents (non-confidential information)

Constituent	**Typical concentration**	**Concentration range**	**Remarks**
Formaldehyde	35 – 55%	No information	

Table 7: Impurities (non-confidential information)

Impurities	**Typical concentration**	**Concentration range**	**Remarks**
Formic acid (CAS N° 64-18-6)	ca 0.3% w/w	No information	Current Annex VI entry: Skin Corr. 1A – H314 SCL: C ≥ 90 % : Skin Corr. 1A; H314 10 % ≤ C < 90 % : Skin Corr. 1B; H314 2 % ≤ C < 10 % : Skin Irrit. 2; H315, Eye Irrit. 2; H319
Iron compounds	<= 0.0001% w/w	No information	No information on the kind of iron compounds found as impurities in formaldehyde.

Traces of lead (0.1 mg/l), sulphur (<5 mg/l) and chlorine (<5 mg/l) are also reported in some formaldehyde solutions used as test substances (Soffritti 1989 and 2002).

Table 8: Additives (non-confidential information)

Additives	Typical concentration	Concentration range	Remarks
Methanol (CAS N° 67-56-1)	ca 2% w/w	No information	Used as a stabiliser Current Annex VI entry: Flam. Liq. 2 - H225 Acute Tox. 3 * - H331 Acute Tox. 3 * - H311 Acute Tox. 3 * - H301 STOT SE 1 – 370** SCL: C ≥ 10 % : STOT SE 1; H370 3 % ≤ C <10 % : STOT SE 2; H371

6,6'-(m-phenylene) bis (1,3,5-triazine-2,4-diamine) (CAS N° 5118-80-9) is also mentionned as an additives (OCDE 2002) but this statement cannot be checked in absence of any information on its function as an additive and it is not known whether it is an additive or an impurity in the meaning of REACH.

1.2.1 Composition of test material

Relevant information is given in the respective study summaries when available.

1.3 Physico-chemical properties

Formaldehyde is a very volatile gas at room temperature (high vapour pressure), very soluble in water but not stable.

When dissolved into water, formaldehyde converts to methanediol $H_2C(OH)_2$, a diol. Aqueous solutions of formaldehyde are referred to as formalin. A typical commercial grade formalin may contain 10–12% methanol in addition to various metallic impurities. The diol also exists in equilibrium with a series of short polymers (called oligomers), depending on the concentration and temperature.

The infinite polymer formed from formaldehyde is called paraformaldehyde.

Table 9: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Nearly colourless pungent, suffocating gas	HSDB (interrogation 2010)	Formaldehyde solution is a clear, colorless or nearly colorless liquid having a pungent, irritating odor
Melting/freezing point	melting point: - 92°C freezing point: -117°C (formaldehyde 37% inhibited)	CRC Handbook of chemistry and Physics, 2006 HSDB (interrogation 2010)	
Boiling point	-19.1 °C	CRC Handbook of chemistry and Physics, 2006	
Relative density	1.067 (Air = 1) Density: 0.815 g/cm^3 at –20°C	HSDB (interrogation 2010) CRC Handbook of chemistry and Physics, 2006	
Vapour pressure	88 556 Pa at – 22,29°C 101 325 Pa at – 19,5°C	CRC Handbook of chemistry and Physics, 2006	Measured Summary of literature
Surface tension	No data		
Water solubility	Very soluble in water (up to 55% at 25°C) 1220 g/L at 25°C	CRC Handbook of chemistry and Physics, 2006	Tends to polymerise and precipitate in aqueous solution from 30% at room temperature if not stabilised.
Partition coefficient n-octanol/water	0.35 at 25°C	CRC Handbook of chemistry and Physics, 2006	Experimental
Flash point	85°C (gas) 50°C (Formaldehyde 37%, 15% methanol, solution)	HSDB (interrogation 2010)	Closed cup
Flammability	Flammable liquid when exposed to heat or flame; can react vigorously with oxidizers. The gas is a more dangerous fire hazard than the vapor.	HSDB (interrogation 2010)	
Explosive properties	Not explosive because of chemical structure. Forms explosive mixture with air. Explosivity limits: lower: 7% upper: 73% Flammable liquid when exposed to heat or	HSDB (interrogation 2010)	

	flame. When aqueous formaldehyde solutions are heated above their flash points, a potential for an explosion hazard exists		
Self-ignition temperature	Auto-ignition temperature: 424°C	HSDB (interrogation 2010)	
Oxidising properties	Readily polymerize at room temperature when not inhibited.		
Granulometry	Not relevant		
Stability in organic solvents and identity of relevant degradation products	Formaldehyde reacts violently with 90% performic acid. Reactions with peroxide, nitrogen dioxide, and performic acid, cause explosions. Decomposition products: carbon monoxide and carbon dioxide	HSDB (interrogation 2010)	
Dissociation constant	pKa = 13,27 at 25°C	HSDB (interrogation 2010)	
Viscosity	Not relevant for the gas		

To convert concentrations in air (at 25°C) 1 ppm = 1.23 $mg/m^3$and 1 mg/m^3 = 0.81 ppm

2 MANUFACTURE AND USES

2.1 Manufacture

Formaldehyde is produced industrially by the catalytic oxidation of methanol.

2.2 Identified uses

Industrial/occupational : starting material in chemical synthesis, intermediate in the chemical industry for the production of condensed resins for the wood, paper and textile processing industry, reagent used for tissue preservation and in embalming fluids in autopsy rooms and pathology departments, disinfectant in operating rooms.

General public: detergents, disinfectants and cleaning agents, building and insulating material, paints and lacquers, adhesives, preservative in cosmetics.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination) (OECD 2002)

Formaldehyde (FA) is a highly water-soluble gas and under normal conditions, it is expected that formaldehyde in ambient air is absorbed through inhalation in the upper respiratory tract. In rats, 93% of the dose is retained in the nasal passage regardless of airborne concentrations. Differences in breathing patterns across species may lead to differences in absorption and distribution. In rats, almost all inhaled formaldehyde is absorbed in the nasal passage, whereas in primates, some absorption occurs in the trachea and proximal regions of the major bronchi (Monticello 1989).

From *in vitro* experiments using human skin, it is estimated that the absorption of a concentrated solution of formalin through the skin amounted to 319 µg/cm2 per hour.

After inhalation of radioactive formaldehyde by the rat, the radioactivity is distributed in the tissues, with the highest concentration in the oesophagus, followed by the kidney, liver, intestines, and lung and was due to metabolic incorporation of formaldehyde.

Formaldehyde is an endogenous metabolite with measurable levels in body fluids and tissues in mammalian systems. Although formaldehyde is a gas at room temperature, it hydrates rapidly and is in equilibrium with its hydrated form methanediol. Formaldehyde is rapidly metabolised to formate mainly subsequently to formation of a FA–glutathione conjugate. Formate is metabolised and either incorporated via normal metabolic pathways into the one-carbon pool or further oxidised to carbon dioxide and exhaled.

Formaldehyde may also react with biological macromolecules at the site of contact if detoxification pathways are overwhelmed and produce DNA-protein and probably protein-protein cross-links. In rats, depletion of glutathione in the nasal cavity was associated with an increase of covalently bound formaldehyde in the nasal mucosa.

Several studies have measured by GC-MS blood concentration of formaldehyde further to inhalation exposure:

- In F-344 rats (n=8/group) exposed to 14.4 ppm (17.3 mg/m^3) for 2 hours, a blood concentration of 2.25±0.07 µg/g was measured immediately after the end of exposure in exposed animals vs 2.24±0.07 µg/g in controls (not significant) (Heck 1985).
- In Rhesus monkeys (n=3) exposed to 6 ppm (7.2 mg/m^3) for 6 h/d, 5d/week for 4 weeks, formaldehyde blood concentration was measured 7 minutes and 45 h after the last exposure. There was no statistical difference between the two measures: 1.84±0.15 µg/g after 7 min and 2.04±0.40 in µg/g after 45 h (p=0.33) (Casanova 1988).

- In humans, 6 volunteers (2 women and 4 men) were exposed to 1.9 ppm formaldehyde (2.3 mg/m^3) for 40 minutes under controlled conditions. No difference was found between blood concentration of formaldehyde before exposure (2.61±0.14 µg/g) and immediately after exposure (2.77±0.28 µg/g). For some individuals, blood concentration of formaldehyde raised after exposure while it decreased in others suggesting that formaldehyde blood concentration may vary with time (Heck 1985).

It is noted that GC-MS actually measured both formaldehyde as such and in its solubilised form methanediol (Heck 1982). Absence of an increase in blood concentration further to inhalation is probably due to its deposition principally within the respiratory tract and its rapid metabolism in the nasal mucosa. In animal species, the half-life of formaldehyde administered intravenously ranges from approximately 1 to 1.5 min in the circulation.

After inhalation of radioactive formaldehyde in the rat, radioactivity is mainly exhaled as carbon dioxide during the 70-h post-exposure period (40%) and excreted in the urine (17%). 35-39% remained in the tissues presumably as products of metabolic incorporation in macromolecules (Heck, 1985). It was further demonstrated that the radioactivity incorporated in the blood and bone marrow further to inhalation of [^{14}C] FA was due to metabolic incorporation and not to covalent binding (Casanova-Schmitz 1984).

A mathematical model for the absorption and metabolism of formaldehyde in humans (Franks 2005) have determined that at inhaled concentration of 1.9 ppm, the flux of formaldehyde to the blood increases rapidly at the beginning of exposure, reaching a constant magnitude within a few seconds. The predicted amount of inhaled formaldehyde entering the blood is relatively small, i.e. 0.00044 mg/l, with the remainder having been removed by other processes such as enzymatic and non-enzymatic reactions. This is calculated to correspond to 2.42 x 10^{-7} mg/l of free formaldehyde, the remaining being methanediol. These results are consistent with the absence of variation of blood endogenous concentrations being around 2.74±0.14 mg/l further to exposure to 1.9 ppm for 40 min in 6 volunteers (Heck 1985). The predicted increase represents only 0.016% of this pre-exposure value. The simulation of exposure to 1.9 ppm for 8 hr/day, 5 days/week predicted a constant maximum concentration in the blood at the same level, with a quick removal (probably few minutes, value not given in the publication) from the blood post-exposure.

Considering an exposure range of 0.1-10 ppm, the concentration in the blood was found to obey a linear relationship with the inhaled concentration of formaldehyde. Even at the highest exposure concentration, the amount entering the blood was extremely small and insignificant compared to pre-exposure endogenous levels (data not shown in the publication).

4.2 Acute toxicity

Not evaluated in this dossier.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not evaluated in this dossier.

4.4 Irritation

Not evaluated in this dossier.

4.5 Corrosivity

Not evaluated in this dossier.

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

Not evaluated in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

A very large database of studies investigating mutagenicity of formaldehyde is available. The most recent and critical studies were reviewed based on the publications. However, the inclusion of others studies in the present dossier relies on the information evaluated and quoted in the OECD SIDS (2002). These latter studies are identified in the reference column with an asterisk (*). Some studies are also industry studies that are described on the basis of the information given in the robust study summary in the registration dossier. They are identified in the table below with the sign # .

4.9.1 Non-human information

4.9.1.1 In vitro data

Table 10: *In vitro* data

Test	Cell type	Conc. (mg/l)	Meta-bolic activity	Observations and Remarks	Ref.
MICRO-ORGANISMS					
Prophage induction, SOS repair test, DNA strand breaks, cross links	pUC13 plasmid	0.0075 mg/l	No	Positive	Kuykendall 1992*
Prophage induction, SOS repair test, DNA strand breaks, cross links	E. coli	20 mg/l	No	Positive	Le Curieux 1993*
Reverse mutation (test substance: FA 37%, measured to be 33%)	TA 98, TA 100, TA 1535 and TA 1537	1-333 µg/plate	With and without (Liver S9 from Aroclor 1254-induced male SD rats or Syrian hamsters)	Positive An increase in frequency of mutants was observed in TA 100 without activation, with rat and with hamster S9.	Haworth 1983
Reverse mutation	TA 97, TA 98, TA 100, TA 102 and TA 104	Approx 0.3 to 1.7 µmoles/plate	No	Positive TA 102 and TA 104 were more sensitive to FA-induced mutagenesis.	Marnett 1985
Reverse mutation (test substance: FA, 37% with 10% methanol)	TA 100	Approx 0.05-1.5 mM	With and without (Liver S9 from Clophen A50-induced male W rats)	Positive. FA induced an increase in the frequency of revertants both with the plate incorporation and the pre-incubation methods. Increases were higher in presence of S9 mix (1.7 fold increase vs 1.3 in the plate incorporation assay and 2.7 vs 1.6 in the pre-	Schmid 1986

				incubation assay). Highest mutants frequency were observed around 0.2 mM in the preincubation method and 1.0 mM in the plate incorporation method. Frequency declined at higher doses due to cytotoxicity of FA.	
Forward or reverse mutation	E. coli K12	18.8 mg/l	No	Positive	Graves 1994*
Reverse mutation (test substance: purity not given)	TA 102	Up to 5 mg/l	With and without	Negative (2/5 trials with S9-mix with invalide positive controls.)	BASF 1986 #
Reverse mutation	TA 102	10 mg/l	No	Positive	Le Curieux 1993*
Reverse mutation	TA 100 TA 102 TA 98	9.3 35.7 17.9 µg/ml	No	Positive	O'Donovan 1993*
Reverse mutation	TA 1535 TA 1537 TA 1538	143 mg/l	No	Negative	O'Donovan 1993*
Reverse mutation	TA 102	0.1-0.25 µg/plate	No	Positive	Chang 1997*
Reverse mutation	TA 102	6.25-50 µg/plate	No	Positive	Dillon 1998*
Reverse mutation	TA 7005 (his^+)	2 µg/plate	No	Positive	Ohta 2000*

Reverse mutation (Ames II)	TAMix (TA 7001- TA 7002 – TA 7003 – TA 7004 – TA 7005- TA 7006) (base pair substitution) TA 98 (frameshift)	4.44-4400 µg/ml	With and without (Liver S9 from Aroclor 1254-induced rats)	Positive without S9 in TAMix but not TA 98.	Kamber 2009
Reverse mutation	E. coli WP2	35.7 mg/l	No	Positive	O'Donovan 1993*
Reverse mutation	E. coli WP3104P	5 µg/plate	No	Weakly positive	Ohta 1999*
Reverse mutation	E. coli WP3104P	2 µg/plate	No	Positive	Ohta 2000*
Homozygosis by mitotic combination or gene conversion	S. cerevisiae	18.5 mg/l	No	Positive	Zimmer-mann 1992*
Forward mutation	N. crassa (heterokoyons, H-12 and H-59 strains)	0.01%	No	Positive	De Serres 1999*
Micronucleus	T. pallida	250 ppm/6hr	No	Positive	Batahla 1999*
MAMMALIAN CELLS (except human cells)					
DNA-adducts	Calf thymus DNA	0.1-50 mM	No	Positive. In presence of GSH, a DNA-adduct of the GSH-FA conjugate was identified.	Lu 2009

DNA-protein cross-links (test substance: FA, purity not given)	Rat tracheal epithelial cell line C18	100-400 µM (90 min)	No	Positive Treatment with FA reduced cell culture growth only at 400 µM for 90 min. The increase of X-ray-induced DNA retention in the alkaline elution assay is used as a measure of DPX. Concentration-related increase in DNA retention from 100 µM indicative of DPX. Treatment with proteinase K prior to elution suppress the effect. Removal of DPX was evident 4 hr post-treatment and most DPX were eliminated 16 hr post-treatment.	Cosma 1988
DNA-protein cross-links	Chinese hamster ovary cells	0.25-59 mM (7.5-1770 mg/l)	No	Positive	Olin 1996*
DNA-protein cross-links	Male B6C3F1 mouse, female CD1 mouse, male F344 rat hepatocytes	Not given	Yes	Weakly positive	Casanova 1997*

DNA-protein cross-links (test substance: FA, purity not given)	Chinese hamster V79 cells	0.125-0.5 mM (3.75-15 mg/l)	No	Positive The reduction of γ-ray-induced DNA migration in the Comet assay is used as a measure of DPX (modified Comet assay). Decrease in DNA migration significant ($p<0.05$) from 0.25 mM indicative of DPX. 24 hr after FA treatment, there is no inhibition of DNA migration, indicating complete removal of DPX.	Merck 1998
DNA-protein cross-links (Comet assay) (test substance: FA, purity not given)	Mouse lymphoma L5178Y cells $tk^{+/-}$	31.25-500 µM for 2 h (0.9-15 mg/l)	No	Positive for DPX Decrease in radiation-induced DNA migration significant indicative of DPX.	Speit 2002
DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	Chinese hamster V79 cells	0.001-200 µM (0.03-6000 µg/l)	No	Positive for DPX Significant decrease ($p<0.05$) in DNA migration under modified conditions (35 min alkaline treatment and 25 min electrophoresis) at 10 and 200 µM, indicative of DPX. Post-treatment with proteinase K under the standard conditions slightly enhanced DNA migration in controls and FA-treated cultures and abolished cross-linking effect of FA. Three-time repeated treatments caused enhancement of cross-linking effects with 3-hr intervals but no effect was identified with 24-hr interval indicating repair of DPX during this interval.	Speit 2007

DNA strand breaks (test substance: FA, purity not given)	Rat tracheal epithelial cell line C18	100-400 µM (90 min)	No	Positive Treatment with FA reduced cell culture growth only at 400 µM for 90 min. The reduction of DNA retention in the alkaline elution assay after treatment with proteinase K prior to elution (to remove DPX) is used as a measure of single strand breaks (SSB). Concentration-related decrease in DNA retention indicative of SSB. The removal of SSB was rapid and complete with no SSB detected 2 hr post-treatment.	Cosma 1988
DNA strand breaks	Rat hepatocytes	22.5 mg/l	No	Positive	Demkowic-Dobrzanski 1992*
DNA strand breaks (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	Chinese hamster V79 cells	0.001-200 µM (0.03-6000 µg/l)	No	Negative No statistical differences in tail moment under standard conditions (25 min alkaline treatment and 25 min electrophoresis). DNA migration with proteinase K treatment was not statistically significantly increased compared to control group with buffer indicating no induction of strand breaks.	Speit 2007
DNA repair (UDS)	Syrian hamster embryo cells	0.3-3 mg/l	No	Positive	Hamaguchi 2000*

Sister chromatid exchange (test substance: FA, purity not given)	Chinese hamster ovary cells	0.2-16 µg/ml	With and without (Liver S9 from Aroclor 1254-induced male SD rats)	Positive. Induction of SCE was questionably positive in one laboratory and clearly positive in the second.	Galloway 1985
Sister chromatid exchange (test substance: FA, purity not given)	Chinese hamster V79 cells	0.0125-0.125 mM (0.375-3.75 mg/l)	No	Positive Significant dose-related increase in SCE (p<0.01) from 0.125 mM.	Merck 1998
Sister Chromatid Exchange (test substance: FA 37% in solution with 7-13% methanol)	Syrian hamster embryo cells	0-33 µM (0-1 mg/l)	No	Positive SCEs per cell were 9.27±3.26, 9.30±3.34, 12.27±4.08** and 18.13± 7.51** at concentrations of 0, 3.3, 10 and 33 µM, respectively (**p<0.01).	Miyachi 2005
Sister Chromatid Exchange (test substance: FA 16%, ultrapure, methanol free)	Chinese hamster V79 cells	0.001-200 µM (0.03-6000 µg/l)	No	Positive Significant increase (p<0.05) in SCE from 100 µM, with a significant decrease of proliferation index at 200 µM.	Speit 2007

Sister Chromatid Exchange (test substance: FA 16%, ultrapure, methanol free)	Chinese hamster V79 cells	50-300 µM	No	Positive Significant concentration-related increase in SCE from 100 µM. Induction of SCE is clearly decreased if BrdUrd is added in the medium 4 hr instead of 1 hr after the FA-exposure, indicating partial repair. V79 cells were also co-cultured for 1 hr with A549 cells, which have been treated with FA for 1 hr either in the exposure medium or after change of the medium at the end of FA exposure of A 549 cells. A significant increase in SCE ($p<0.05$) was detected from 50 µM in V79 cells maintained in the same medium after 1hr of co-culture but not when culture medium was changed.	Neuss 2008
Chromosomal aberration	Chinese hamster cells	6.5 mg/l	With and without	Positive	Natarajan 1983*
Chromosomal aberration (test substance: FA, purity not given) (tests performed by two different laboratories)	Chinese hamster ovary cells	1.1-50 µg/ml	With and without (Liver S9 from Aroclor 1254-induced male SD rats)	Positive. A high level of chromosomal damages was observed in one laboratory with S9 at doses that caused toxicity. A positive result was also observed without S9 in one laboratory at the highest dose but not in the second laboratory that tested lower doses.	Galloway 1985

Micronucleus (test substance: FA, purity not given)	Chinese hamster V79 cells	0.0125-0.25 mM (0.375-3.75 mg/l)	No	Positive Significant dose-related increase in SCE (p<0.01) from 0.125 mM.	Merck 1998
Micronucleus (test substance: FA 16%, ultrapure, methanol free)	Chinese hamster V79 cells	0.001-200 µM (0.03-6000 µg/l)	No	Positive Significant increase (p<0.01) in MN from 75 µM. Three-time repeated treatments caused enhancement of MN induction with 3-hr intervals but not with 24-hr interval.	Speit 2007
Gene mutation	Chinese hamster V79 cells	9 mg/l (0.3 mM)	No	Positive	Grafström 1993*
Gene mutation (HPRT locus) (test substance: FA, purity not given)	Chinese hamster V79 cells	0.0125-0.5 mM	No	Negative HPRT-mutant frequency was not increased after FA treatment with expression time of 5, 7 or 9 days. Positive control gave an appropriate response.	Merck 1998

Gene mutation (test substance: formalin: 37% FA stabilised with 10% methanol)	Mouse lymphoma L5178Y cells	0.008-0.020 ml/l without S9 0.040-0.065 ml/l with S9	With and without (Liver S9 from Aroclor 1254-induced male SD rats)	Positive. A dose-related increase in mutant frequency and reduction of total growth was observed both with and without S9. No statistical analysis was performed but a more than a threefold increase of mutant frequency was reported from 0.008 ml/l without S9 (52.3% of total growth at this dose) and from 0.045 ml/l with S9 (55.8% of total growth at this dose). Addition of FA deshydrogenase (FDH) that instantly transforms FA into formic acid suppress the mutagenic and cytotoxic effects at all doses. Two commercial FA-releaser biocides, the FA conjugate methenamine, a synthetic resin coating containing FA-conjugate as crosslinking agent were also tested and produced at different level of doses mutants and cytotoxicity in absence but not in presence of FDH. It confirms that mutagenicity is related FA.	Blackburn 1991
Gene mutation	Mouse lymphoma L5178Y cells (MTBE activated)	0.065 mg/l (2.2 µM) (37% sol.)	Yes	Positive	Mackerer 1996*

Gene mutation (test substance: FA, purity not given)	Mouse lymphoma L5178Y cells	62.5-250 µM for 2 h (OCDE 476 recommends 3-6 hr)	No	Positive. Dose-related increase in the frequency of mutants from 62.5 µM with a 7-fold increase at 250 µM compared to spontaneous frequency. Dose-related increase in the frequency of small colony mutants, suggestive of chromosomal aberrations and only marginal increase in the frequency of large colonies. Positive control (4-NOQ) gave the appropriate response. Whole chromosome fluorescence in situ hybridisation was used to further elucidate the mechanism of chromosome mutations and indicate mainly deletions or recombinations.	Speit 2002
HUMAN CELLS					
DNA-protein cross-links	Lung/bronchial epithelial cells	12 mg/l	No	Positive	Grafström 1990*
DNA-protein cross-links	Fibroblasts	0.25-59 mM	No	Positive	Olin 1996*
DNA-protein cross-links	White blood cells	0.1-1 mM	No	Positive	Shaham 1996*
DNA-protein cross-links	EBV-BL lymphoma cells	0.01-0.03 mg/l	No	Positive	Costa 1997*
DNA-protein cross-links	Gastric mucosa cells	1mM	No	Positive	Blasiak 2000*

DNA-protein cross-links (test substance: methanol-stabilised solution of FA)	Human cell lines: HF/SV fibroblasts, kidney Ad293, lung A549 cells + human lymphocytes	0.02 mM	No	Positive DPX half life in the three human cell lines was similar and averaged 12.5 hr. Removal of DPX from peripheral human lymphocytes was slower (averaged half-life of 18.1 hr). Hydrolysis of DPX was due both to spontaneous hydrolysis and to active repair, active repair being less efficient in lymphocytes than in human cell lines.	Quievryn 2000
DNA-protein cross-links	Lymphocytes	0.1 mM	No	Positive	Andersson 2003*
DNA protein crosslinks	Human skin keratinocytes and fibroblasts	0, 12.5, 25, 50, 100 µM for 8 h	No	Positive for DPX. The induction of DPX was measured by the ability of FA to reduce DNA migration in the Comet assay induced by MMS (250 µM MMS for 2.5 h after FA exposure). Significant crosslink formations observed in both cell types from 25 µM with linear increase up to 100 µM.	Emri 2004

DNA-protein cross-links, repair (Comet) Test substance: 10% formalin	Human peripheral blood lymphocytes (1 sample) and Hela cell lines	5-625 µM	No	Positive No significant increase in DPX coefficient at 5 and 25 µM but significant dose-related increase at concentration ≥ 50 µM in both human peripheral lymphocytes and Hela cell lines. In Hela cell lines at the non cytotoxic concentration of 50 µM, a statistically significant decrease in DPX coefficient was observed when FA was removed from cell culture for ≥ 18 hr, indicating progressive repair of DPX.	Liu 2006
DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	Human blood samples	25-300 µM	No	Positive Significant concentration-related decrease ($p<0.05$) in gamma ray (2 Gy) induced DNA migration from 25 µM, indicating induction of DPX. When cells are irradiated at different time points after treatments, reduction of gamma ray induced DNA migration decreased with time. At 100µM, DPX are completely removed after 8 hr, while a portion of DPX still persists after 24 hr at 200 and 300 µM.	Schmid 2007

DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	A549 epithelia-like human lung cell lines and human nasal epithelial cells	100-300 µM	No	Positive A concentration-related induction of DPX was induced in A549 cells after treatment for 1 or 4 hr. After 4 hr incubation in fresh medium, a reduction of the crosslinking effect is was seen and complete removal after 8 hr. A concentration-related induction of DPX was induced in human nasal epithelium cells after treatment for 1 hr. After 4 hr incubation in fresh medium, a reduction of the crosslinking effect was seen and DNA migration was not significantly decreased after 8 hr in fresh medium.	Speit 2008
DNA-protein cross-links, repair Test substance: 10% formalin	HepG2 cells (human liver carcinoma cell line)	25-50-75-100 µM for 1 hr Repair experiment: 75 µM for 1 hr (+0, 6, 12, 18, 24h of incubation after removal of FA)	No	Positive Significant dose-related increase of the DPX coefficient at concentration ≥ 75 µM. In the repair experiment, the DPX coefficient was significantly decreased and similar to control after 18 hr or more. DPX coefficient was determined as the ratio of the percentage of the DNA involved in DPX over the percentage of the DNA involved in DPX + unbound fraction of DNA	Zhao 2009

DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	A549 epithelia-like human lung cell lines	50-300 µM	No	Positive A concentration-related induction of DPX was induced in A549 cells after treatment for 1 hr, significant at 200 µM and above. With three repeated 1-hr exposures with 24-hr or 48-hr intervals, the crosslinking effect of FA was clearly enhanced at 200 and 300 µM. Preexposure to low level of FA-concentrations (50 µM) does not influence the crosslinking effect of a high FA-concentration or DPX removal.	Speit 2010
DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	Primary human nasal epithelial cells (HNEC) from 3 women	100-200 µM	No	Positive for DPX A concentration-related induction of DPX was induced in HNEC cells after treatment for 1 hr, significant from 100 µM. After 4 hr incubation in fresh medium, a reduction of the crosslinking effect was seen and DNA migration was not significantly decreased after 8 hr in fresh medium.	Neuss, 2010a

DNA-protein cross-links (Comet assay) (test substance: FA 16%, ultrapure, methanol free)	Primary human nasal epithelial cells (HNEC) and human lymphocytes	100-300 µM	No	Positive in lymphocytes and HNEC directly exposed to FA, negative in lymphocytes co-cultured with exposed HNEC in absence of FA in the medium. In lymphocytes treated for 1 hr, significant concentration-related decrease ($p<0.05$) in gamma ray (2 Gy) induced DNA migration from 100 µM, indicating induction of DPX. Lymphocytes were co-cultured for 1 or 4 hr with HNEC, which have been treated with FA for 1 hr, either in the exposure medium or after change of the medium at the end of FA exposure of HNEC. A significant concentration-related decrease ($p<0.05$) in gamma ray induced DNA migration was detected from 100 µM in HNEC exposed for 1 hr and maintained in the same medium after 4 hr of co-culture. Only a slight cross-linking effect was detected when the exposure medium was removed for co-cultivation for 4 hr. A significant concentration-related decrease ($p<0.05$) in gamma ray induced DNA migration was detected from 100 µM in lymphocytes maintained in the same medium after both 1hr or 4 hr of co-culture. FA concentration was measured to decrease with time in the presence of cells with around 75% of the initial concentration measured after 4 hr at 100 µM.	Neuss 2010b

				No significant effect was detected in lymphocytes co-cultured with HNEC when the medium was changed before co-cultivation. No significantly increased amounts of FA were detectable in the new medium after 5, 15, 30 min, and 1, 4 or 8 hr	
DNA repair	keratinocytes and fibroblasts	10 µM prior to UV irradiation	No	Positive for inhibition of DNA repair. Disturbed repair kinetics after UVC and UVB, but not after UVA irradiation: single-strand breaks disappeared 6 h after solely UVC (3 mJ/cm2) or 3 h after solely UVB (30 mJ/cm2) exposure but were still present at these time points in presence of formaldehyde.	Emri 2004
DNA strand breaks	Lung/bronchial epithelial cells	12 mg/l	No	Positive	Grafström 1990*
DNA strand breaks	Lung/bronchial epithelial cells	1 mM	Yes	Positive	Vock 1999*

DNA strand breaks (Comet) Test substance: 10% formalin	Human peripheral blood lymphocytes (1 sample) and Hela cell lines	5-625 µM	No	Positive In the Comet assay, tail moment was statistically increased at 5 and 25 µM but decreased rapidly with increasing concentrations above 25 µM in human peripheral lymphocytes. A similar peak was observed at 10 µM in Hela cell lines. The author concluded that FA induces strandbreaks at low concentrations and crosslinks at higher concentrations. Tail moment in Hela cell lines decreased with time after FA removal from 30 min (concentration not given) and reached a plateau similar to controls after 90 min.	Liu 2006
Sister chromatid exchange (test substance: FA, 37% with 10% methanol)	Lymphocytes	0.032-1.0 mM	With and without (Liver S9 from Clophen A50-induced male W rats)	Positive Dose-dependant increase in SCE frequency that was significant from 0.125 mM with and without S9. Methanol alone (0.1-0.2 mM with S9 mix) did not increase SCE frequency.	Schmid 1986
Sister Chromatid Exchange (test substance: FA 16%, ultrapure, methanol free)	Human blood samples	25-200 µM	No	Positive Significant increase ($p<0.05$) in SCE at 200 µM, with a significant decrease of proliferation index at this dose.	Schmid 2007
Sister Chromatid Exchange (test substance: FA 16%, ultrapure, methanol free)	Epithelial-like human lung cells line (A549)	50-300 µM	No	Positive Significant concentration-related increase in SCE from 100 µM.	Neuss 2008

Chromosomal aberration (test substance: FA, 37% with 10% methanol)	Lymphocytes	0.032-1.0 mM	With and without (Liver S9 from Clophen A50-induced male W rats)	Positive Dose-dependant increase in chromatid breaks and gaps that was significant from 0.25 mM with S9 and 0.5 mM without S9. Singnificant increase in chromatid exchange at 0.5 mM without S9. Cell proliferation was reduced from 0.5 mM with and without S9. Addition of albumin tot he culture medium did not change the results. Methanol alone (0.1-0.2 mM with S9 mix) did not increase chromosomal aberration frequency.	Schmid 1986
Chromosomal aberration (test substance: formalin 38% with 10-14% methanol)	Lymphocytes	0.5-8 µg/L	No	Positive Decrease in mitotic index from 6 µg/L. Statistical significant increase in aberrations including gaps from 6 µg/L and in aberration excluding gaps from 8 µg/L. Aberrations consisted mainly in chromatid deletions and exchanges.	Boots company 1986#
Micronucleus	MRC5CV normal cells, XP124 OSV XP cells, GMO6914 FA cells	125-500 µM	No	Positive	Speit 2000*

Micronucleus (test substance: FA 16%, ultrapure, methanol free)	Human blood samples	100-400 µM	No	Positive in some experimental conditions. When blood cultures were treated with FA at the start of the culture, no significant increase in MN up to 250 µM in presence of cyto-toxicity at 250 µM based on the measure of the nuclear division index. When blood cultures were treated with FA 24 hr after the start of the culture, no significant increase in MN up to 400 µM in presence of cytotoxicity at 400 µM. When blood cultures were treated with FA 44 hr after the start of the culture, a significant concentration-related increase in MN from 300 µM was observed in presence of cytotoxicity from 300 µM. At 350 µM, slides were analysed by FISH. 81% of analysed MN in binucleated cells were centromere-negative and 19% centromere-positive (55% of centromere-negative in controls).	Schmid 2007

Gene mutation (HPRT locus)	TK6 human lymphoblast	150 µM (8 sequential exposures of 2 hr)	No	Positive Treatment with FA induced a mutant frequency of $23x10^{-6}$ (12-fold higher than controls). 30 mutants were analysed by Northen and Southern blot. 6/30 mutants had completely lost the hprt gene. 8/30 had partial deletion of the gene DNA. None of these mutants produced RNAm. 16/30 mutants had point mutation (no visible alteration with southern blot). RNAm of 6 of these mutants contained a single base-pair substitution at AT base pairs and 4 at the same site. The remaining mutant was lacking exon 8. In comparison with spontaneous mutations FA lead to a shift from point mutations in favour of complete deletion.	Liber 1989
Gene mutation (HPRT locus)	Bronchial fibroblast/epithelial cells	3 mg/l	No	Positive	Grafström 1990*

Microarray analyses (test substance: FA 16%, ultrapure, methanol free)	Primary human nasal epithelial cells (HNEC) from 3 women	50-100 µM for 2h 50-200 µM for 4 h 100-200 µM for 24 h 4 x 20-50 µM with 24 h intervals	No	A two-fold variation in the expression of 153 and 887 genes was observed at 100 µM and 200 µM for 4 h, respectively. No significant effect was seen with treatment for 2 h or for 24 h. Repeated treatments with 50 µM changed gene expression of 143 genes. Genes up-regulated involved most frequently the biological processes of "transcription", "translation", "nucleosome assembly" and "negative regulation of transcription from RNA polymerase II promoter". The expression of genes involved in FA detoxification and DNA repair were not significantly altered.	Neuss, 2010a

4.9.1.2 In vivo data

4.9.1.2.1 Somatic cells at sites of contact

Table 11: Experimental *in vivo* data at the site of contact

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA adducts (test substance: heated radiolabelled paraformaldehyde – purity not specified)	Fischer 344 rats (male) (n=5/8)	Nasal respiratory epithelium	Inhalation: 10 ppm for 6 hr or 5 days (6hr/d) (nose-only)	Positive Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected after both 1 or 5 days of exposure (2.84± 1.13 at 5 days) - Exogenous: detected after both 1 or 5 days of exposure (1.28± 0.49 at 1 day and 2.43± 0.78 at 5 days) Detection of N^6-hydroxy-methyl-dA adducts: - Endogenous: detected after both 1 or 5 days of exposure (3.61± 0.95 at 5 days) - Exogenous: not detected. Detection of dG-CH_2-dG crosslinks: - Endogenous: detected after both 1 or 5 days of exposure (0.18± 0.06 at 5 days) - Exogenous: detected after both 1 or 5 days of exposure (0.14± 0.06 at 1 day and 0.26± 0.07 at 5 days)	Lu 2010

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA adducts (test substance: radiolabelled formaldehyde – purity not specified)	Rats (n=3-5/group)	Bone marrow	Inhalation: 0.7, 2.0, 5.8, 9.1 or 15.2 ppm for 6hr	Positive Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected (similar levels across groups; mean: 4.7± 1.8 adducts/10^7 dG) - Exogenous: detected at all concentrations: 0.04±0.02, 0.19±0.08, 1.04±0.24, 2.03±0.43, and 11.15±3.01 adducts/ 10^7 dG at 0.7, 2.0, 5.8, 9.1, and 15.2 ppm)	Lu 2011
DNA adducts (test substance: radiolabelled formaldehyde – purity not specified)	Cynomolgus macaque (n=4/group)	Nasal maxilloturbinate	Inhalation: 1.9 or 6.1 ppm for 2 days (6hr/d) (whole body)	Positive Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected (2.05±0.54 adducts/10^7 dG at 6.1 ppm) - Exogenous: detected at both concentrations (0.26± 0.04 at 1.9 ppm and 0.41± 0.05 at 6.1 ppm)	Moeller 2011
DNA-protein cross-links	Rats	Nasal respiratory mucosa	Inhalation: 0.3, 0.7, 2, 6, or 10 ppm for 6 hr	Positive At 6 ppm, ^{14}C radioactivity was detected in DNA. Approximately 91% was attributed to metabolic incorporation (by analysis of the $^{3}H/^{14}C$ ratio). Additional radioactivity was attributed to the formation of DPX. In the dosimetry experiment, DPX were detected at all concentrations from 0.3 ppm.	Casanova 1989

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA-protein cross-links	Rhesus monkeys	Respiratory tract	Inhalation: 0.7, 2 or 6 ppm for 6hr	Positive. Concentrations of cross-links were highest in the mucosa of the middle turbinates, lower in the anterior lateral wall/septum and nasopharynx and very low in the larynx, trachea and in the proximal portions of the major bronchi of some monkeys exposed to 6 ppm. No cross-links were detected in the maxillary sinuses or lung parenchyma.	Casanova 1991*
DNA-protein cross-links	Rats (n=10/group)	Nasal mucosa: LM= lateral meatus (high tumour region) and M:PM = medial and posterior meatus (low tumour region)	Acute DPX yield: Inhalation: 0, 0.7, 2, 6, or 15 ppm for 6 hr/d for 81 days (whole body) + 3 hr to 0.7, 2, 6, or 15 ppm $H^{14}CHO$ (nose-only) with or without pre-exposure Cumulative DPX yield: Inhalation: 0, 6, or 10 ppm for 6 hr/d for 81 days (whole body) + 3 hr to 6 or 10 ppm (nose-only) with or without pre-exposure	Positive Acute DPX yields increased non linearly with concentration and were approximately sixfold greater in the LM than in the M:PM at all concentrations in non pre-exposed rats. From 6 ppm, acute DPX yields in the LM were greater in non pre-exposed rats than in pre-exposed rats. It may be explained by dilution of DPX due to hyperplasia, a possible increased detoxification of FA or repair of DPX. For cumulative DPX yields, no significant accumulation of DPX has occurred in pre-exposed rats as evidenced by lower interfacial DNA compared to non pre-exposed rats (indicating poor extractability of DNA from protein and yield of DPX). Light microscopy revealed multifocal epithelial hypertrophy, hyperplasia and squamous metaplasia in the nasal mucosa of rats exposed to 6, 10 or 15 ppm. The lesions observed were most severe in the LM and on the nasal septum adjacent to the	Casanova 1994

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
				middle medial meatus. A significant increase in cell proliferation (indicated by incorporation of $H^{14}CHO$ into DNA) was observed in the LM of rats pre-exposed to 6 and 15 ppm but not in rats that were not pre-exposed indicating enhanced cell proliferation following subchronic exposure. In the M:PM cell proliferation was significantly increased only at 15 ppm and to a lesser extent than in the LM. When rats were not pre-exposed, cell proliferation was slightly higher in the M:PM than in LM (not significantly) indicating that DNA synthesis may be inhibited by FA (from 6 ppm).	
DNA-protein crosslinks (Comet)	F-344 rats (n=6/group)	Broncho-alveolar lavage cells	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Negative Using standard protocols with subsequent irradiation to identify potential DPX, no statistical effect on tail moment was observed.	Neuss 2010c
Comet (test substance : formaldehyde, no information on purity)	Sprague-Dawley rats (n=30/group)	Lung cells	Inhalation: 0, 5 and 10 ppm, 6 hr/d, 5 d/wk for 2 weeks	Positive Olive tail moments were 0.75±0.07, 1.11±0.17* and 1.32±0.34* in animals exposed to 0, 5 and 10 ppm, respectively (*p<0.05). In this study, a significant increase in lipid peroxidation (measured by malondi-aldehyde) and in protein oxidation (measured by determination of the content of carbonyl groups on amino acids) were detected at 10 ppm.	Sul 2007

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA damage (Comet)	F-344 rats (n=6/group)	Broncho-alveolar lavage cells	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Negative Tail moments using standard protocols were 0.38±0.11, 0.41±1.58, 0.78±0.59, 0.24±0.02, 0.27±0.19, 0.37±0.14 and 0.53±0.50 in animals exposed to 0, 0.5, 1, 2, 6, 10 and 15 ppm, respectively (no statistical difference). Positive control gave appropriate response.	Neuss 2010c
Chromosomal aberration (test substance: paraformaldehyde heated – purity not specified)	Sprague-Dawley rats (n=5 males /group)	Broncho-alveolar lavage cells (50 cells/ animals; sampling time not specified)	Inhalation: 0, 0.5, 3, or 15 ppm, 6 hr/d, 5 d/wk, for 1 and 8 weeks (whole-body)	Positive at 15 ppm. Dose-related increase in frequency of chromosomal aberrations, predominantly chromatid breaks. Statistically significant ($p<0.05$) at 15 ppm only after both 1 or 8 weeks of exposure: 7.6 and 9.2% of the scored cells had chromosomal aberrations following 1 and 8 weeks of exposure, respectively, with control levels of 3.5 and 4.8%, respectively.	Dallas 1992
Micronucleus	Rats	Gastro-intestinal tract	Oral: 200 mg/kg	Positive in all tissues (stomach, duodenum, ileum, colon) in conjunction with signs of severe local irritation	Migliore 1989*
Micronucleus (test substance: purity 10% aqueous solution)	Male Wistar rats (n=3/group)	Nasal epithelial cells	Inhalation: 0 or 20 ppm, once 6 hr/d	Negative Positive controls in this study (FA + IP injection of 10 mg/kg CPA) were not valid.	BASF 2001a#
Micronucleus (test substance: purity 9.99% aqueous solution)	Male Wistar rats (n=3/group)	Nasal epithelial cells	Inhalation: 0 or 20 ppm, 6 hr/d for 5 days	Negative Positive controls in this study (FA + IP injection of 200 mg/kg CPA) were not valid. Focal erosions and ulcerations associated with a distinct purulent inflammation and increased cell proliferation were observed in the respiratory and transitional epithelium.	BASF 2001b#

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
Micronucleus	F-344 rats (n=6/group)	Broncho-alveolar lavage cells	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Not conclusive Mean MN frequency were1.50±1.67, 1.58±1.83, 1.58±1.94, 0.75±1.76, 1.17±2.25, 2.33±1.03 and 2.00±2.09 in animals exposed to 0, 0.5, 1, 2, 6, 10 and 15 ppm, respectively (no statistical difference). No increase in MN frequency was however observed in the positive control (10 mg/kg/d cyclophosphamide twice orally). There is no validated protocol and positive control of reference for the micronucleus assay in BAL cells by inhalation and the positive control used may not be appropriate (route and dose of exposure).	Neuss 2010c
p53 mutations	F344 rats	Nasal squamous cell carcinomas (n=11 tumours)	Inhalation: 15 ppm, 6 hr/day, 5d/wk, for 2 years	DNA sequencing of the *p53* DNA from the rat tumours examined showed point mutations in 5 of 11 of the tumours. All of the mutated codons observed have been mutated in human cancers.	Recio 1992

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
p53 and *K-Ras* mutations	F344/NCrl rats	Nasal mucosa (lateral meatus and nasoturbinate)	Inhalation: 0, 0.7, 2, 6, 10 and 15 ppm, 6 hr/day, 5d/wk, for 13 weeks	Negative Mutation prevalence (percentage of samples with mutant fraction above 10^{-5}) for *p53* codon 271 CAT mutation: 0 ppm: 40% 0.7 ppm: 20% 2 ppm: 0% 6 ppm: 40% 10 ppm: 20% 15 ppm: 40% Mutation prevalence for *K-Ras* codon 12 GAT mutation was 0% in all control and treated groups as mutant frequency were extremely low. Cell replication increased with dose in the nasal epithelium with labelling index of 18%, 22%, 35%, 38%, 51%* and 64%* for the 0, 0.7, 2, 10 and 15 ppm groups, respectively. (* p<0.01)	Meng, 2010

4.9.1.2.2 Somatic cells at distant sites

Table 12: Experimental *in vivo* data in somatic cells at distant sites

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA adducts (test substance: heated radiolabelled paraformaldehyde – purity not specified)	Fischer 344 rats (male) (n=4/5)	Blood, spleen, thymus, lung, liver, bone marrow	Inhalation: 10 ppm for 6 hr or 5 days (6hr/d) (nose-only)	Negative Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected in all tissues after both 1 or 5 days of exposure (1.17± 0.35 in bone marrow and 1.10±0.28 in blood at 5 days) - Exogenous: not detected in any tissue Detection of N^6-hydroxy-methyl-dA adducts: - Endogenous: detected in all tissues after both 1 or 5 days of exposure (2.99±0.08 in bone marrow and 3.66±0.78 in blood at 5 days) - Exogenous: not detected in any tissue. Detection of dG-CH_2-dG crosslinks: - Endogenous: detected in all tissues after both 1 or 5 days of exposure (0.11± 0.03 in bone marrow and 0.10±0.07 in blood at 5 days) - Exogenous: not detected in any tissue	Lu 2010
DNA adducts (test substance: radiolabelled formaldehyde – purity not specified)	Rats (n=3-5/group)	Bone marrow	Inhalation: 15.2 ppm for 6hr	Negative Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected (≈15 adducts/10^7 dG) - Exogenous: not detected	Lu 2011

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA adducts (test substance: radiolabelled formaldehyde – purity not specified)	Cynomolgus macaque (n=4/group)	Bone marrow	Inhalation: 1.9 or 6.1 ppm for 2 days (6hr/d) (whole body)	Negative Detection of N^2-hydroxy-methyl-dG adducts: - Endogenous: detected (12.4 ± 3.6 adducts/10^7 dG at 6.1 ppm) - Exogenous: not detected	Moeller 2011
DNA-protein crosslinks Test substance: 10% formalin	Kun Ming male rats (n=6/group)	Liver cells	Inhalation: 0, 0.4, 0.8 and 2.4 ppm continuously for 72 hr Repair experiment: 2.4 ppm for 72 hr (+0, 6, 12, 18 or 24 hr of recovery)	Positive Significant and dose-related increase in DPX coefficient at 0.8 and 2.4 ppm. In the repair experiment, the DPX coefficient was significantly decreased after 6 hr or more. Repair was complete after 12 hr.	Zhao 2009
DNA damage and DNA-protein crosslinks (Comet)	F-344 rats (n=6/group)	Blood cells	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Negative Under standard conditions, tail moments were 0.19±0.07, 0.24±0.11, 0.22±0.11, 0.16±0.03, 0.13±0.03, 0.17±0.11 and 0.17±0.03 in animals exposed to 0, 0.5, 1, 2, 6, 10 and 15 ppm, respectively (no statistical difference). Positive control gave appropriate response. In combination with gamma-irradiation of blood samples (2 Gy), no statistically significant difference was observed in rats exposed to FA, indicating that DPX are not present as DNA irradiation-induced migration is not reduced.	Speit 2009

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
DNA damage (Comet) Test substance: FA (purity not specified)	Sprague Dawley male rats (n=10/ group)	Lymphocytes and liver	Inhalation: 0, 5 or 10 ppm, 6 hr/d, 5d/wk for 2 weeks	Positive Olive tail moment in lymphocytes: Controls: 1.24±0.04 5 ppm: 1.72±0.11, p=0.0019) 10 ppm: 2.16±0.14, p=0.0001) Olive tail moment in liver cells: Controls: 1.19±0.08 5 ppm: 1.73±0.10, p=0.0001) 10 ppm: 2.49±0.20, p=0.0001) In this assay, peroxidation of lipids and oxidation of proteins was observed at 10 ppm in lymphocytes and liver cells. Expression of 32 plasma proteins was up or down regulated. Analysis of the expression of plasma cytokines showed a dose related upregulation of IL-4 and down regulation of IFN-gamma suggesting an inflammatory effect.	Im 2006
Sister Chromatid Exchange	Mice (n=10/ sex in 1st exp. and 5/sex in the 2nd)	Bone marrow	Inhalation: 1st experiment : 0, 6, 12 or 25 ppm, 6 hr/d for 5 days 2nd experiment: 0, 5, 10, 15 or 25 ppm, 6 hr/d for 5 days	Equivocal Positive in females et 12 and 25 ppm but not in males in the 1st experiment. Negative in males and females in the second experiment but SCE frequency in controls was unusually high. Only 20 cells per animal analysed.	Formaldehyde Institute 1982#
Sister Chromatid Exchange	Mice (n=5/ sex)	Bone marrow	Inhalation: 1st experiment : 0, 6, 12 or 25 ppm, 6 hr/d for 4 days	Negative Positive in females et 12 and 25 ppm but not in males in the 1st experiment. Negative in males and females in the second experiment but SCE frequency in controls was unusually high. Only 50 cells per animal analysed.	Formaldehyde Institute 1982#

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
Sister Chromatid Exchange	Rats	Leucocytes	Inhalation: 0.5, 6, or 15 ppm, 6 hr/d for 5 days	Negative	Kligerman 1984*
Sister Chromatid Exchange	F-344 rats (n=4-6/group)	Peripheral blood	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Negative SCE frequency were 4.58±0.60, 4.94±0.53, 4.76±0.27, 4.92±0.42, 4.84±0.40, 4.77±0.92 and 5.02±0.18 in animals exposed to 0, 0.5, 1, 2, 6, 10 and 15 ppm, respectively (no statistical difference). Positive control gave appropriate response.	Speit 2009
Chromosomal aberration	Rats	Leucocytes	Inhalation: 0.5, 6, or 15 ppm, 6 hr/d for 5 days	Negative	Kligerman 1984*
Chromosomal aberration	Rats	Bone marrow	Inhalation: 0.5 and 1.5 mg/m^3 (4hr/d for 4 mo) equivalent to 0.4 and 1.2 ppm.	Positive (both doses). No information on dose-response.	Kitaeva 1990 (in Russian)
Chromosomal aberration (test substance: paraformaldehyde heated – purity not specified)	Sprague-Dawley rats (n=5 males /group)	Bone marrow (50 cells/ animals; sampling time not specified)	Inhalation: 0, 0.5, 3, or 15 ppm, 6 hr/d, 5 d/wk, for 1 and 8 weeks (whole-body)	Negative	Dallas 1992
Chromosomal aberration	Mice	Spleen cells	Intraperitoneal 6.25, 12.5 or 25 mg/kg once	Negative	Natarajan 1983*
Micronucleus	Mice	Femoral polychromatic erythrocyte	Intraperitoneal 6.25, 12.5 or 25 mg/kg once	Negative	Natarajan 1983*
Micronucleus (Test substance: purity 37%)	CD-1-mice (n=5 males / group)	Polychromatic erythrocytes in bone marrow Reticulocytes in peripheral blood	Gavage : 2 applications of 0, 100, 200 mg/kg Gavage: 25, 50, 100, 200 mg/kg and i.v. : 2 applications of 0, 10, 20, 30 mg/kg	Negative. No incresase in micronuclei in any treatment group in bone marrow (24 and 72 hr after applications) and peripheral blood after gavage or i.v. injection (0, 24, 48 and 72 hr after application).	Morita 1997

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
Micronucleus	F-344 rats (n=5-6/group)	Peripheral blood	Inhalation: 0, 0.5, 1, 2, 6, 10 and 15 ppm, 6 hr/d, 5 d/wk for 4 weeks	Negative Mean MN frequency were 0.22±0.18, 0.18±0.12, 0.32±0.23, 0.23±0.21, 0.14±0.11, 0.23±0.21 and 0.22±0.04 in animals exposed to 0, 0.5, 1, 2, 6, 10 and 15 ppm, respectively (no statistical difference). Positive control gave appropriate response.	Speit 2009

4.9.1.2.3 Germ cells

Table 13: Experimental *in vivo* data in germ cells

Test	Species	Exposure route & Harvest time	Observations and remarks	Ref
Sex-linked recessive lethal mutations	D. melanogaster	420 mg/l	Positive	Alderson 1967*
Heritable translocation	D. melanogaster	420 mg/l	Positive	Khan 1967*
Sister chromosome exchange	Mice (male)	Intraperitoneal injection of 0, 0.2, 2 or 20 mg/kg for 5 days. Sacrifice at the 6th and 14th day.	Positive. Significant increase of SCE ratio in germ cells in the two highest doses groups.	Tang 2003 (in Chinese)
Chromosomal aberration	Mice	Single intraperitoneal injection of 50 mg/kg	Negative	Fontinie-Houbrechts 1981*
Micronucleus	Mice (male)	Intraperitoneal injection of 0, 0.2, 2 or 20 mg/kg for 5 days. Sacrifice at the 6th and 14th day.	Positive. Significant increase of MN ratio in early spermatogenic cells in the two highest doses groups.	Tang 2003
Dominant lethal mutation assay	Rats (female)	Inhalation: 0.5 and 1.5 mg/m^3 (4hr/d for 4 mo) equivalent to 0.4 and 1.2 ppm	Weakly positive (at 1.5 mg/m^3)	Kitaeva 1990 (in Russian)

Dominant lethal mutation assay	Mice	Single intraperitoneal injection of 20 mg/kg	Negative	Epstein 1968*
Dominant lethal mutation assay	Mice	Single intraperitoneal injection of 20 mg/kg	Negative	Epstein 1972*
Dominant lethal mutation assay	Mice	Single intraperitoneal injection of 50 mg/kg	Weakly positive	Fontinie-Houbrechts 1981*
Dominant lethal mutation assay	Albino rats (n=12 males/group)	Intraperitoneal injection of 0, 0.125, 0.250 and 0.6 mg/kg for 5 days	Positive. Dose-related decrease in fertile matings 1-7 and 8-14 days after male treatment but not 15-21 days after from 0.125 mg/kg. Significant dose-related increase in the number of dead implants per female when mated 1-7 and 8-14 days after male treatment from 0.250 mg/kg.	Odeigah 1997

Induction of mutations on Expanded Simple Tandem Repeats (ESTR) Test substance: 37% formalin	Rats (n=15 males/group)	Inhalation: 0, 2, 20 and 200 mg/m^3 for 2 hours (single exposure) equivalent to 0, 1.6, 16 and 160 ppm Six weeks post-exposure, male mice were mated with females. Five days following mating sperm was extracted from cauda epididymis. Somatic genome DNA was extracted from tail tissue of both parents and at least 6 pups from each litter. DNA fingerprints were generated by hybridisation with 3 different ESTR probes	Positive Breeding rates, litter size and body weight of pups were not affected by treatment. Mutation rate in the somatic genome DNA of offspring was increased in a dose-dependent manner for the three probes. <u>Mutation rate for Ms6-hm probe:</u> 0 mg/m^3: 0.079 (95% CI: 0.036-0.149) 2 mg/m^3: 0.115 (95% CI: 0.059-0.201), p=0.491 20 mg/m^3: 0.148 (95% CI: 0.079-0.253), p=0.171 200 mg/m^3: 0.173 (95% CI: 0.101-0.278), p=0.057 P trend = 0.0294 <u>Mutation rate for Hm-2 probe:</u> 0 mg/m^3: 0.073 (95% CI: 0.039-0.125) 2 mg/m^3: 0.106 (95% CI: 0.059-0.174), p=0.325 20 mg/m^3: 0.129 (95% CI: 0.086-0.187), p=0.071 200 mg/m^3: 0.188 (95% CI: 0.135-0.255), p=0.001 P trend = 0.0005 <u>Mutation rate for MMS10 probe:</u> 0 mg/m^3: 0.074 (95% CI: 0.057-0.096) 200 mg/m^3: 0.141 (95% CI: 0.115-0.170), p=0.000 Parent sperm genome DNA mutation rate was only found increased in the group exposed to 200 mg/m^3 when all locus were combined. <u>Mutation rate for total single locus:</u> 0 mg/m^3: 0 2 mg/m^3: 0 20 mg/m^3: 0 200 mg/m^3: 0.244 (95% CI: 0.117-0.449) P trend = 0.0005	Liu 2009

4.9.2 Human information

4.9.2.1 Studies performed at the site of contact

Table 14: Human data at the site of contact

Test	Tissue	Population	Exposure	Observations and remarks	Ref
Micro-nucleus	Respiratory nasal mucosa cells	Exposed: 15 non-smoking workers (plywood factory) Controls : 15 subjects	Mean levels: about 0.1-0.39 mg/m^3 (equivalent to 0.08 – 0.31 ppm) + exposure to low levels of wood dust (0.23 to 0.73 mg/m^3).	Positive. Higher frequency of micronucleated cells in the exposed group (0.90 ± 0.47 vs. 0.25 ± 0.22, *Mann-Whitney U* test: p < 0.01). Cells with more than one micronucleus were not found.	Ballarin 1992*
Micro-nucleus	Buccal and nasal mucosa cells	29 mortician students (22 males, 9 females) during a course of embalming for 9 weeks sampled at the beginning and at the end of the course.	Average cumulative exposure: 14.8 ppm-h with an average concentration during embalming of 1.4 ppm, peak exposure up to 6.6 ppm and an average of 6.9 embalmings per subject.	Positive in buccal cells only Epithelial buccal cells: pre-exposure: 0.046±0.17 ‰ post-exposure: 0.60±1.27 ‰, p<0.05 Positive dose-response with cumulative exposure in men but not in women. Epithelial nasal cells: pre-exposure: 0.41±0.52 ‰ post-exposure: 0.05±0.67 ‰, p=0.26 No dose response was seen.	Suruda 1993
Micro-nucleus	Exfoliated buccal and nasal cells	28 mortuary science students sampled before and after a 90-day embalming class (19 subjects for buccal cells and 13 for nasal cells) (re-analysis of slides from Suruda 1993)	Mean exposure: buccal cells group: 14.8±7.2 ppm-h; nasal cells group: 16.5±5.8 ppm-h	Positive in buccal cells only. Increased micronuclei frequency in buccal cells (0.6‰ before to 2‰ after exposure, p=0.007) but not in nasal cells (2‰ to 2.5‰, p=0.2) The increase in MN frequency was greater for centromere-negative than for centromere positive MN.	Titenko-Holland 1996

Micro-nucleus	Nasal and oral mucosa cells, lympho-cytes	25 anatomy students sampled before and after the period of exposure	Exposure: 0.508±0.299 mg/m^3 (equivalent to 0.41±0.24 ppm) for 3h, 3 times/week for 8 weeks	Positive. Increased micronuclei frequency in nasal (3.84±1.48 vs 1.2±0.67, p< 0.001) and oral (0.857±0.558 vs 0.568±0.317, p< 0.01) cells but not in lymphocytes (0.913±0.389 vs 1.11±0.543).	Ying 1997
Micro-nucleus	Nasal mucosa cells	Exposed: 23 individuals in pathology and anatomy laboratories. Controls: 25 healthy subjects	Exposure to 2-4 ppm Duration: 1-13 years (mean: 5.06 years)	Positive. The mean values of nasal mucosa micronucleus frequency from exposed and controls were 1.01±0.62 and 0.61±0.27‰, respectively (p < 0.01).	Burgaz 2001
Micro-nucleus	Exfoliated buccal cells	Exposed: 28 anatomy and pathology laboratory workers Controls: 18 male university staff	Exposure to 2-4 ppm	Positive. Increased mean micronucleated cells frequency in exposed workers: 0.71±0.56% vs 0.33±0.30% in controls (p<0.05).	Burgaz 2002
Micro-nucleus	Nasal mucosa cells (from nasal septum)	Exposed: 18 non-smoking workers from a FA factory and 16 non-smoking waiters exposed to indoor FA in a newly fitted ballroom. Controls: 23 non-smoking subjects	Exposure about 1 ppm (TWA 8h) for workers (mean duration: 8.5 years) and 0.1 ppm (TWA 5h) for waiters (duration: 12 weeks)	Positive. Mean nasal mucosa micronucleus frequency: Controls: 1.25±0.65‰, Workers: 2.70±1.50‰, p< 0.05 No significant increase in waiters (approximate mean of 1.7‰).	Ye 2005

Micro-nucleus	Exfoliated buccal mucosa cells	Exposed: 21 volunteers (10 women, 11 men) sampled for buccal smear 1 week before the start of the study (control 1), at the start of the study (control 2), at the end of the exposure period of 10 days and 7, 14 and 21 days thereafter.	Exposure under strictly controlled conditions 4 h per day over a period of 10 working days. Exposure varied randomly each day from constant 0.15 ppm up to 0.5 ppm with four peaks of 1.0 ppm for 15 min each (13.5 ppm h cumulative exposure over 10 working days). FA was masked on four days by co-exposure to ethyl acetate. During exposure, subjects had to perform bicycle exercises (about 80 W) three times for 15 min.	Negative No significant increase in the frequency of MN was measured at any time point after the end of the exposure. The apparent slight non-significant increase in MN observed at the end of exposure was caused by elevated frequencies of MN in two subjects only. Twenty-one days after the end of the exposure MN frequencies were significantly lower in comparison with control 1.	Speit 2007

Micro-nucleus	Exfoliated buccal mucosa cells	Exposed: 80 workers occupationally exposed to FA (30 from FA and FA-based resins production factory and 50 from pathology and anatomy laboratory) Controls: 85 non-exposed subjects	Exposure in industrial workers: mean TWA of 0.21 ppm with mean ceiling concentration of 0.52 ppm for a mean duration of 6.74 years. Exposure in laboratory workers: mean TWA of 0.28 ppm with mean ceiling concentration of 2.52 ppm for a mean duration of 9.12 years.	Positive. Mean nasal mucosa micronucleus frequency: Controls: 0.13±0.48‰, Industrial workers: 1.27±1.55‰, p<0.001 Laboratory workers: 0.64±1.74‰, p<0.005 A moderate positive association was observed with duration of exposure (r=0.209, p<0.05). Control and exposed groups did not differ in age and smoking habits but a larger number of women were included in the control group (63.5 vs 40%). Gender was however not found to have a significant impact on frequency of micronuclei.	Viegas 2010
Micro-nucleus	Nasal mucosa cells	Exposed : 41 male non-smoking volunteers sampled before the first exposure, after the last exposure and 1, 2 and 3 weeks after the end of exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day from 0 ppm or 0.3 ppm with four peaks of 0.6 ppm for 15 min, or 0.4 with four peaks of 0.8 ppm for 15 min, or 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	Negative. Samples from 33 to 36 volunteers were analysed (56 000 to 62 000 cells per data point). Mean micronucleus frequency was 0.21±0.35‰ before exposure, 0.27±0.42‰ post-exposure, 0.24±0.43‰ one week after, 0.24±0.45‰ two weeks after and 0.17±0.41‰ three weeks after. Analysis of variance did not indicate a significant difference between groups (p=0.8664).	Zeller 2011

Gene expression (micro-array)	Nasal biopsies	Exposed : 20 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day from 0 ppm or 0.3 ppm with four peaks of 0.6 ppm for 15 min, or 0.4 with four peaks of 0.8 ppm for 15 min, or 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	The expression of up to 17 genes was altered with at least a two-fold change.	Zeller 2011

4.9.2.2 Studies performed at distant sites

Table 15: Human data at distant sites

Test	Tissue	Population	Exposure	Observations and remarks	Ref
FA-DNA adduct	Leukocytes	Exposed: 32 smokers of 10 cigarettes per day Controls: 30 non-smokers	Exposure to formaldehyde via smoking. Mainstream cigarette smoke contains 14 to 28 µg/cigarette of FA.	91% of smokers and 23 % of non-smokers were positive for the FA-DNA adduct N^6-hydroxymethyldeoxyadenosine (p<0.001; detection limit: 10 fmol/µmol dAdo) Mean N^6-OHdAdo (fmol /µmol dAdo): smokers: 179±205 non-smokers: 15.5±33.8, p<0.001	Wang 2009a

DNA-protein crosslinks	Mono-nuclear cell fraction of peripheral blood	Exposed: 186 workers from 14 hospital pathology departments Controls: 213 administrative workers of the same hospitals	1-51 years of exposure (mean 15.9 years) Low-exposure: 0.04-0.7 ppm (mean: 0.4) High-exposure: 0.72-5.6 ppm (mean: 2.24)	Positive. Increased mean amount of DNA-protein crosslinks in the total exposed group compared to controls (0.21 vs 0.14, $p<0.01$). No significant difference between the low- and high-exposure groups. Adjustment was made for age, sex, education and origin.	Shaham 2002
DNA repair	Peripheral lymphocytes	Exposed: 37 women working in pathology department (16 exposed to FA and other solvents and 21 exposed mainly to FA). Controls: 37 healthy women from health service staff without known exposure to FA or other genotoxic agents.	Measurements of FA concentrations in ambient air within the last 3 years were available for 3 of the 4 sites and were similar: 0.23-1.20 mg/m^3 (0.19-0.97 ppm) for hospital 2 and 0.63-1.10 mg/m^3 (0.51-0.89 ppm) for hospital 3 and 0.40-1.21 mg/m^3 (0.32-0.98 ppm) for university pathology department. Mean duration of exposure of 21.8±2.0 years in the group exposed to FA and other solvents and 17.7±1.9 years in the group exposed to FA only.	Negative <u>UV-induced UDS (arbitrary units)</u> Controls: 6.47±0.41 FA+other solvents: 5.04±0.62 FA only: 4.73±0.86 * $p<0.05$ A statistically significant increase in apoptosis was measured in subjects exposed to FA+other solvents and in subjects exposed to FA only. An increase in cell proliferation was also observed and was significant in subjects exposed to FA only when measured by the lectin labelling index but not by % of cells in S-phase or expression of the cell-activation marker CD71 on T-lymphocytes.	Jakab 2010

Comet assay	Peripheral lymphocytes	Exposed: 30 workers from hospital pathological anatomy laboratories Controls: 30 non-exposed employees matched by age, sex, lifestyle and smoking habits working in the same area in administrative offices.	Mean levels of formaldehyde in the workers breathing zone was 1.50 and 4.43 ppm during macroscopic examination of preserved specimens and during disposal of waste solutions and specimens. Mean individual 8h-exposure was 0.44 ppm (range: 0.04-1.58 ppm)	Positive Mean tail length (µm): Controls: 41.85±1.97 (range:28.85-66.52) Exposed: 60.00±2.31** (range:33.76-99.09) **p<0.05 A positive correlation was found between exposure levels and tail length (r=0.333, p=0.005). No significant effect of age, smoking habits or duration of exposure. Females had a statistically significant increased tail length than males in the exposed group but not in controls. It is noted that use of Trypan Blue to assess cytotoxicity and absence of ghost cells counting may have underestimated apoptotic phenomena.	Costa 2008
Comet assay	Peripheral lymphocytes	Exposed: 151 workers from two plywood factory in China Controls: 112 non-exposed workers from a machine manufactory.	TWA exposure ranged from 0.10-7.88 mg/m^3 (0.08-6.38 ppm) in exposed workers versus < 0.01 mg/m^3 (0.008 ppm) in controls.	Positive Frequency of Olive Tail Moment: Controls: 0.93 (0.78-1.10) Low-FA exposure: 3.03 (2.49-3.67) High-FA exposure: 3.95 (3.53-4.43) Differences were statistically significant (p<0.05) A positive trend was found between exposure levels and olive tail moment.	Jiang 2010 (similar to Yu 2005)

Comet assay	Peripheral lymphocytes	Exposed: 41 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day from 0 ppm or 0.3 ppm with four peaks of 0.6 ppm for 15 min, or 0.4 with four peaks of 0.8 ppm for 15 min, or 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	Equivocal. No change in Olive Tail Moment before and after exposure (0.30±0.12 vs 0.33±0.12) but small but statistically significant increase in Olive Tail Intensity after exposure (2.28±0.49 vs 2.66±0.94, p=0.002).	Zeller 2011
DNA damage (chemiluminescence microplate or 3D (damaged DNA detection) assay	Peripheral lymphocytes	57 pathology and anatomy laboratory workers from 5 hospitals DNA damage was measured before and after the shift.	Mean concentration were 2.0 (range: <0.1-20.4 ppm) for sampling time of 15 min (during supposed highest exposing tasks) and 0.1 ppm (range: <0.1-0.7 ppm) during a 8h-typical day. Duration: 0.5-34 years (mean: 13.2 years)	Negative No difference in DNA damage at the beginning and at the end of a working day. DNA damage was correlated neither with the work practice nor with personal air sampling data.	Orsière 2006
Sister-chromatid exchange	Peripheral lympho-cytes	Exposed: 6 pathology workers Controls: 5 unexposed subjects		Negative. No detectable differences between the groups in sister-chromatid exchange frequencies.	Thomp-son 1984*

Sister-chromatid exchange	Peripheral lympho-cytes	Exposed: 20 male papermakers Controls: 20 male workers from the same factory	FA outside the papermachine did not exceed 0.2 ppm. Workers enter the paper machine for short times with level of exposure up to 3 ppm. Very rarely, areas with FA up to 20-50 ppm had to be entered for 1-5 min. Duration of of exposure: 2–30 years with aa average of 14.5±7.2 years	Negative. SCE/cells: Exposed workers: 8.87±0.24 Unexposed workers: 9.53±0.35 Smokers had higher SCE frequencies but no significantly higher SCE values were observed for smoking or for non-smoking exposed- workers compared with the corresponding control subjects.	Bauchinger 1985
Sister-chromatid exchange	Peripheral lympho-cytes	8 non-smoking anatomy students sampled before and after the period of exposure	mean concentration of 1.2 ppm (1.5 mg/m^3) during a10-week anatomy class	Positive. Small (*P* = 0.02) increase in sister-chromatide exchange after exposure.	Yager 1986*
Sister chromatid exchange	Peripheral lymphocytes	29 mortician students (22 males, 9 females) during a course of embalming for 9 weeks sampled at the beginning and at the end of the course.	Average cumulative exposure: 14.8 ppm-h with an average concentration during embalming of 1.4 ppm and an average of 6.9 embalmings per subject.	Negative SCE/cell: pre-exposure: 7.72±1.26 ‰ post-exposure: 7.14±0.89 ‰ No dose response with cumulative exposure was seen.	Suruda 1993
Sister chromatid exchange	Peripheral lympho-cytes	Exposed: 13 anatomy students Controls: 10 unexposed students (similar age and sex) All subjects were non-smokers.	3.17 mg/m^3 (2.37 ppm), 10 h per week for 12 weeks	Positive. Increased sister chromatide exchange frequency (p<0.05) (5.91±0.71 vs 5.26±0.51 in controls, p<0.05)	He 1998

Sister chromatid exchange	Peripheral lympho-cytes	23 anatomy students (non-smoking) sampled before and after the period of exposure	0.508±0.299 mg/m^3 (0.41±0.24 ppm), for 3h, 3 times/week for 8 weeks	Negative. No significant difference on lymphocyte proliferation rate and sister-chromatid exchange (6.383±0.405 vs 6.613±0.786 after exposure).	Ying 1999
Sister chromatid exchange	Peripheral lympho-cytes	Exposed: 90 workers from 14 hospital pathology departments Controls: 52 administrative workers from the same hospitals	1-39 years of exposure (mean 15.4 years) Low-exposure group: mean level: 0.4 ppm High-exposure group: mean level: 2.24 ppm	Positive. Increased mean number of SCE per chromosome (0.27 in exposed workers vs 0.19 in controls, $p<0.01$) Increased proportion of high frequency cells (0.88 vs 0.44, $p<0.01$). Adjustment was made for sex, education, origin and smoking. No difference between the low- and high-exposure groups.	Shaham 2002
Sister chromatid exchange	Peripheral lymphocytes	Exposed: 18 non-smoking workers from a FA factory and 16 non-smoking waiters exposed to indoor FA. Controls: 23 non-smoking subjects	Exposure about 1 ppm (TWA 8h) for workers (mean duration: 8.5 years) and 0.1 ppm (TWA 5h) for waiters (duration: 12 weeks)	Positive. Significant increase in SCE frequency in workers ($p<0.05$). No significant increase in waiters. In workers, a significant increase of B cells with decreased total T cells and T-cytotoxic-suppressor cells was observed in the lymphocyte subset analysis.	Ye 2005

Sister chromatid exchange	Peripheral lymphocytes	Exposed: 30 workers from hospital pathological anatomy laboratories Controls: 30 non-exposed employees matched by age, sex, lifestyle and smoking habits working in the same area in administrative offices.	Mean levels of formaldehyde in the workers breathing zone was 1.50 and 4.43 ppm during macroscopic examination of preserved specimens and during disposal of waste solutions and specimens. Mean individual 8h-exposure was 0.44 ppm (range: 0.04-1.58 ppm)	Positive Controls: 4.49±0.16 (range: 3.10-3.06) Exposed: 6.13±0.29** (range: 3.64-8.80) **p<0.05 No effect of gender, age or duration of exposure. Smokers had a statistically significant higher frequency of SCE than non-smokers in controls but not in the exposed group.	Costa 2008
Sister chromatid exchange	Peripheral lymphocytes	36 workers from a Cancer Research Institute working in different department and with different level of exposure.	Exposure to formaldehyde during a typical working day was measured by a diffuse sampler and categorise as low exposure (< 26 µg/m^{3}or 0.02 ppm, mean: 14.7±5.4 µg/m^3, range: 4.9-25.4, 27 subjects) or high exposure (≥ 26 µg/m^3 or 0.02 ppm, mean: 56.2±79.8 µg/m^3, range: 26.3-268.7, 9 subjects).	Negative Frequency of SCE (30 cells analysed by subject): Low exposure: 6.57±1.38 based on 17 subjects High exposure: 5.06±0.76 based on 2 subjects Mean ratio: 0.81 (95% CI: 0.56-1.18), p=0.274 The FA-conjugate to human serum albumin (FA-HAS) was measured as a marker of exposure and subject with high exposure to FA showed a significant increase of FA-HSA (p =0.033).	Pala 2008

Sister chromatid exchange	Peripheral lymphocytes	Exposed: 37 women working in pathology department (16 exposed to FA and other solvents and 21 exposed mainly to FA). Controls: 37 healthy women from health service staff without known exposure to FA or other genotoxic agents.	Measurements of FA concentrations in ambient air within the last 3 years were available for 3 of the 4 sites and were similar: 0.23-1.20 mg/m^3 (0.19-0.97 ppm) for hospital 2 and 0.63-1.10 mg/m^3 (0.51-0.89 ppm) for hospital 3 and 0.40-1.21 mg/m^3 (0.32-0.98 ppm) for university pathology department. Mean duration of exposure of 21.8±2.0 years in the group exposed to FA and other solvents and 17.7±1.9 years in the group exposed to FA only.	Negative <u>SCE</u> Controls: 6.16±0.16 FA+other solvents: 6.14±0.23 FA only: 6.36±0.26 Analysis of smokers and no-smokers independently did not influence the result. <u>High-frequency SCE cells</u> Controls: 3.76±1.14 FA+other solvents: 3.20±1.66 FA only: 7.05±2.19 *p<0.05	Jakab 2010

Sister chromatid exchange	Peripheral lymphocytes	Exposed : 41 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day: 0 ppm, 0.3 ppm with four peaks of 0.6 ppm for 15 min, 0.4 with four peaks of 0.8 ppm for 15 min, 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	Negative No change in number of SCE per metaphase: 6.1±0.90 pre-exposure vs 6.1±0.94 post-exposure.	Zeller 2011
Chromo-somal aberration	Peripheral lympho-cytes	Exposed: 6 pathology workers Controls: 5 unexposed subjects		Negative. No detectable differences between the groups in chromosomal aberration induction.	Thomp-son 1984*

Chromo-somal aberration	Peripheral lympho-cytes	Exposed: 20 male papermakers Controls: 20 male workers from the same factory	FA outside the papermachine did not exceed 0.2 ppm. Workers enter the paper machine for short times with level of exposure up to 3 ppm. Very rarely, areas with FA up to 20-50 ppm had to be entered for 1-5 min. Duration of of exposure: 2–30 years with aa average of 14.5±7.2 years	Positive. Dicentrics chromosome/cells: Exposed workers: 0.0013±0.0003 Unexposed workers: 0.0005±0.0002 $p<0.05$ The significantly increased incidence of dicentrics or dicentrics and ring chromosomes holds only for 11 exposed-workers currently employed as supervisors when supervisor and operators are analysed separetely. Their total mean exposure time was about 2.5 times longer than 9 operators. The mean age of supervisors' group is also higher but is not considered to have influenced the analysis. No effect on chromatid-type aberrations or frequency of gap per cell.	Bauchinger 1985
Chromo-somal aberration	Peripheral lympho-cytes	Exposed: 20 workers of a wood-splinter materials factory Controls: 19 employees of the same plant	8h time-weighted concentrations of 0.55-10.36 mg/m^3 (0.44-8.39 ppm) for 5 to >16 years	Negative. No significant difference between control and exposed groups for any chromosomal anomalies (high levels in the control compared to the general population).	Vargova 1992
Chromo-somal aberration	Peripheral lympho-cytes	Exposed: 30 medical students Controls: 30 matched unexposed subjects	< 1.2 mg/m^3 (1.0 ppm)	Negative. No difference in incidence of chromosomal aberrations between the exposed and control groups.	Vasu-deva 1996

Chromo-somal aberration	Peripheral lympho-cytes	Exposed: 13 anatomy students Controls: 10 unexposed students (similar age and sex) All subjects were non-smokers.	3.17 mg/m^3 (2.57 ppm), 10 h per week for 12 weeks	Positive. Increased chromosomal aberration (breaks and gaps) incidence (5.92±2.4 vs 3.40±1.57 in controls, p<0.01) Correlation of micronuclei and chromosal aberration incidences in exposed subjects.	He 1998
Chromosomal aberrations	Peripheral lymphocytes	36 workers from a Cancer Research Institute working in different department and with different level of exposure.	Exposure to formaldehyde during a typical working day was measured by a diffuse sampler and categorise as low exposure (< 26µg/m^3 or 0.02 ppm, mean: 14.7±5.4 µg/m^3, range: 4.9-25.4, 27 subjects) or high exposure (≥ 26 µg/m^{3}or 0.02 ppm, mean: 56.2±79.8 µg/m^3, range: 26.3-268.7, 9 subjects).	Negative Frequency of CA (100 cells analysed by subject): Low exposure: 2.95±1.79 based on 19 subjects High exposure: 2.22±1.27 based on 5 subjects Mean ratio: 0.83 (95% CI: 0.42-1.64), p=0.588 The FA-conjugate to human serum albumin (FA-HAS) was measured as a marker of exposure and subject with high exposure to FA showed a significant increase of FA-HSA (p =0.033).	Pala 2008

Chromosomal aberrations	Peripheral lymphocytes	Exposed: 37 women working in pathology department (16 exposed to FA and other solvents and 21 exposed mainly to FA). Controls: 37 healthy women from health service staff without known exposure to FA or other genotoxic agents.	Measurements of FA concentrations in ambient air within the last 3 years were available for 3 of the 4 sites and were similar: 0.23-1.20 mg/m^3 (0.19-0.97 ppm) for hospital 2 and 0.63-1.10 mg/m^3 (0.51-0.89 ppm) for hospital 3 and 0.40-1.21 mg/m^3 (0.32-0.98 ppm) for university pathology department. Mean duration of exposure of 21.8±2.0 years in the group exposed to FA and other solvents and 17.7±1.9 years in the group exposed to FA only.	Positive <u>Total chromosome aberrations</u> Controls: 1.62±0.26 FA+other solvents: 4.00±0.55* FA only: 3.05±0.62* <u>Chromatid type aberrations</u> Controls: 1.00±0.20 FA+other solvents: 2.88±0.46* FA only: 2.35±0.46* <u>Gaps</u> Controls: 3.59±0.36 FA+other solvents: 5.94±0.69* FA only: 6.00±0.65* <u>Aneuploidy</u> Controls: 8.89±0.66 FA+other solvents: 4.44±0.48* FA only: 5.40±0.61* <u>Premature centromere division (PCD): separation of centromeres during prophase/metaphase (%)</u> Controls: 7.60±0.84 FA+other solvents: 15.06±1.55* FA only: 13.65±1.59* Weak correlation of PCD with apoptosis and no correlation with chromosomal aberrations. *$p<0.05$ No significant difference in results between subjects with different smoking habits or age. In subjects exposed to FA only, a significant decrease of frequency of chromosomal aberrations was observed in subjects with duration of exposure above the mean compared to subjects with exposure below the mean.	Jakab 2010

Micro-nucleus	Peripheral lymphocytes	29 mortician students (22 males, 9 females) during a course of embalming for 9 weeks sampled at the beginning and at the end of the course.	Average cumulative exposure: 14.8 ppm-h with an average concentration during embalming of 1.4 ppm and an average of 6.9 embalmings per subject.	Positive MN frequency: pre-exposure: 4.95±1.72 ‰ post-exposure: 6.36±2.03 ‰, $p<0.05$ Positive dose-response with cumulative exposure in males but not in females and when smoking and coffee drinking were included in the analysis.	Suruda 1993
Micro-nucleus	Peripheral lympho-cytes	Exposed: 13 anatomy students Controls: 10 unexposed students (similar age and sex) All subjects were non-smokers.	3.17 mg/m^3 (2.57 ppm), 10 h per week for 12 weeks	Positive. Increased micronuclei frequency (6.38±2.5 vs 3.15±1.46‰, $p<0.01$) Correlation of micronuclei and chromosal aberration incidences in exposed subjects.	He 1998
Micro-nucleus	Peripheral lympho-cytes	Exposed: 10 non-smoking women working in a pathology laboratory Controls: 27 non-smoking age-matched women	1.2 ppm (mean) for 1-16 years (mean 9 years)	Positive. Increased rate of micronuclei in lymphocytes (18.8‰ in exposed group vs 8.8‰ in controls, $p<0.05$)	Sari-Minodier 2001
Micro-nucleus	Peripheral lymphocytes	Exposed: 151 workers from two plywood factory in China Controls: 112 non-exposed workers from a machine manufactory.	TWA exposure ranged from 0.10-7.88 mg/m^3 (0.08-6.38 ppm) in exposed workers versus < 0.01 mg/m^3 (0.008 ppm) in controls.	Positive Frequency of MN (/100 binucleated cells): Controls: 0.27±0.13 Low-FA exposure: 0.41±0.25 High-FA exposure: 0.65±0.36 Differences were statistically significant ($p<0.05$) A positive trend was found between exposure levels and frequency of MN.	Jiang 2010 (similar to Yu 2005)

Micro-nucleus	Peripheral lymphocytes	Exposed: 59 pathology and anatomy laboratory workers from 5 hospitals Controls: 37 non-exposed hospital employees that did not differ in age, sex and smoking habits.	Mean concentration were 2.0 (range: <0.1-20.4 ppm) for sampling time of 15 min (during supposed highest exposing tasks) and 0.1 ppm (range: <0.1-0.7 ppm) during a 8h-typical day. Duration: 0.5-34 years (mean: 13.2 years)	Positive Binucleated micronucleated cell rate (‰): Exposed: 16.9±9.3 Controls: 11.1±6.0 **p=0.001** It was also positively correlated with donor age in the exposed population. It was not correlated with personal sampling data. Frequency of centromeric micronuclei was assessed in 18 exposed and control subjects by FISH: Binucleated micronucleated cell rate (‰): Exposed: 19.1±10.1 Controls: 11.9±5.6 **p=0.021** Total number of micronuclei (‰): Exposed: 21.0±12.6 Controls: 14.4±8.1 p=0.084 The number of MN without centromere was not affected by exposure but a non statistically significant increase in MN with centromere was observed in the exposed group (78 % f MN in the exposed group vs 67 in controls). The frequency of micronuclei containing only one centromere was statistically significantly higher (p<0.001) in the exposed group.	Orsière 2006

Micro-nucleus	Peripheral lymphocytes	Exposed: 30 workers from hospital pathological anatomy laboratories Controls: 30 non-exposed employees matched by age, sex, lifestyle and smoking habits working in the same area in administrative offices.	Mean levels of formaldehyde in the workers breathing zone was 1.50 and 4.43 ppm during macroscopic examination of preserved specimens and during disposal of waste solutions and specimens. Mean individual 8h-exposure was 0.44 ppm (range: 0.04-1.58 ppm)	Positive Controls: 3.27±0.69 (range: 0-17) **Exposed: 5.47±076* (range:1-17)** *p<0.003 A positive correlation was found between exposure levels and micronuclei frequency (r=0.384, p=0.001). No significant effect of gender, age, smoking habits or duration of exposure.	Costa 2008
Micronucleus	Peripheral lymphocytes	36 workers from a Cancer Research Institute working in different department and with different level of exposure.	Exposure to formaldehyde during a typical working day was measured by a diffuse sampler and categorise as low exposure (< 26µg/m^{3}or 0.02 ppm, mean: 14.7±5.4 µg/m^3, range: 4.9-25.4, 27 subjects) or high exposure (≥ 26 µg/m^{3}or 0.02 ppm, mean: 56.2±79.8 µg/m^3, range: 26.3-268.7, 9 subjects).	Negative Frequency of MN (2000 cells analysed by subjects): Low exposure: 0.26±0.24 based on 25 subjects High exposure: 0.31±0.17 based on 7 subjects Mean ratio: 1.43 (95% CI: 0.26-7.81), p=0.676 The FA-conjugate to human serum albumin (FA-HAS) was measured as a marker of exposure and subject with high exposure to FA showed a significant increase of FA-HSA (p =0.033). It is noted that MN frequencies reported here are low considering published maximum spontaneous rate of 16/1000 (Van Hummelen 1990)	Pala 2008

Micro-nucleus	Peripheral lymphocytes	Exposed: 80 workers occupationally exposed to FA (30 from FA and FA-based resins production factory and 50 from pathology and anatomy laboratory) Controls: 85 non-exposed subjects	Exposure in industrial workers: mean TWA of 0.21 ppm with mean ceiling concentration of 0.52 ppm for a mean duration of 6.74 years. Exposure in laboratory workers: mean TWA of 0.28 ppm with mean ceiling concentration of 2.52 ppm for a mean duration of 9.12 years.	Positive. Mean micronucleus frequency: Controls: 1.17±1.95‰, Industrial workers: 1.76±2.07‰, not significant Laboratory workers: 3.70±3.86‰, p<0.001 A moderate positive association was observed with duration of exposure (r=0.401, p<0.05). Control and exposed groups did not differ in age and smoking habits but a larger number of women were included in the control group (63.5 vs 40%). Gender was however not found to have a significant impact on frequency of micronuclei.	Viegas 2010
Micro-nucleus	Peripheral lymphocytes	Exposed : 41 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day: 0 ppm, 0.3 ppm with four peaks of 0.6 ppm for 15 min, 0.4 with four peaks of 0.8 ppm for 15 min, 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	Negative No change in micronucleus frequency: 6.5±3.2 pre-exposure vs 5.7±3.3 post-exposure (p=0.118).	Zeller 2011

Genic mutation	Peripheral lymphocytes	Exposed: 37 women working in pathology department (16 exposed to FA and other solvents and 21 exposed mainly to FA). Controls: 37 healthy women from health service staff without known exposure to FA or other genotoxic agents.	Measurements of FA concentrations in ambient air within the last 3 years were available for 3 of the 4 sites and were similar: 0.23-1.20 mg/m^3 (0.19-0.97 ppm) for hospital 2 and 0.63-1.10 mg/m^3 (0.51-0.89 ppm) for hospital 3 and 0.40-1.21 mg/m^3 (0.32-0.98 ppm) for university pathology department. Mean duration of exposure of 21.8±2.0 years in the group exposed to FA and other solvents and 17.7±1.9 years in the group exposed to FA only.	Negative <u>HPRT mutation: variant frequency (x10^6)</u> Controls: 7.75±1.02 FA+other solvents: 6.32±2.04 FA only: 3.68±0.52* * $p<0.05$	Jakab 2010

Genotype analysis	Whole blood	Exposed: 30 workers from hospital pathological anatomy laboratories Controls: 30 non-exposed employees matched by age, sex, lifestyle and smoking habits working in the same area in administrative offices.	Mean levels of formaldehyde in the workers breathing zone was 1.50 and 4.43 ppm during macroscopic examination of preserved specimens and during disposal of waste solutions and specimens. Mean individual 8h-exposure was 0.44 ppm (range: 0.04-1.58 ppm)	Negative Polymorphic genes for xenobiotic metabolising enzymes (glutathione-S-transferases or GST) and DNA repair enzymes were analysed. Null genotypes of GST and polymorphism in the nucleotide excision-repair pathway have been associated with increased risk for several cancers. GSTM1 null genotype: Controls: 48% Exposed: 13% GSTT1 null genotype: Controls: 7% Exposed: 17% No significant effect on the distribution of ERCC1, ERCC4 and ERCC5 genotypes was observed.	Costa 2008
Gene expression (using RT-PCR and TaqMan probes)	Peripheral lymphocytes	Exposed : 41 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day from 0 ppm or 0.3 ppm with four peaks of 0.6 ppm for 15 min, or 0.4 with four peaks of 0.8 ppm for 15 min, or 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	Negative No change in the expression of the GHS-dependent formaldehyde deshydrogenase (ADH5): 2.351±0.50 pre-exposure vs 2.655±0.37 post-exposure.	Zeller 2011

Gene expression (micro-array)	Peripheral lymphocytes	Exposed : 20 male non-smoking volunteers sampled before the first exposure and after the last exposure.	Exposure under strictly controlled conditions 4 h per day over a period of 5 consecutive days. Exposure varied randomly each day from 0 ppm or 0.3 ppm with four peaks of 0.6 ppm for 15 min, or 0.4 with four peaks of 0.8 ppm for 15 min, or 0.5 ppm or 0.7 ppm. During exposure, subjects had to perform bicycle exercises (about 80 W) four times for 15 min.	The expression of up to 9 genes was altered with at least a two-fold change.	Zeller 2011

Analysis of the presence of some cytogenetic changes by FISH	Hematopoietic progenitor cells from peripheral blood (colony-forming-unit-granulocyte-macrophage) (n=150 cells /subject)	Exposed: 10 highly exposed workers selected from workers exposed to FA concentration between 0.6 and 2.5 ppm daily for at least 3 months in a factory producing FA-melanine resins and one factory using resins in China. Controls: 12 unexposed workers from the same geographic region with comparable demographic and socioeconomic characteristics, matched by age and gender. Exposed and controls subjects were not exposed to benzene, radiation or other known hematotoxic agents	Occupational exposure collected by a questionnaire administered by a trained interview. Exposure was monitored for a full shift on 3 working days for each exposed subject. Median exposure concentration: 2.14 ppm (10^{th} percentile: 1.38 ppm; 90^{th} percentile: 4.14 ppm) in exposed subjects *vs* 0.032 ppm in controls.	The frequency of loss of chromosome 7 (p=0.0039) and of trisomy of chromosome 8 (p=0.040) were statistically increased. Loss of chromosome 7 and gain of chromosome 8 are among the most frequent cytogenetic changes observed in myeloid leukaemia. It is however noted that cytogenetic changes were quantified after mixing together the cells that have been cultured for each subject and are not based on the number of clones. A difference in the growth kinetic of each clone may therefore have interfered with quantification.	Zhang 2010

4.9.3 Summary and discussion of mutagenicity

Experimental data

In vitro, numerous studies provide evidence that formaldehyde is a direct genotoxic substance in bacterial, mammalian and various human cell cultures without metabolisation. Positive results are reported in gene mutation assays. Induction of DNA-protein crosslinks (DPX) have been identified in many mammalian and human cell cultures and is the most sensitive DNA damage after formaldehyde exposure. Formaldehyde forms DPX by reacting with the amino or imino groups of proteins (e.g. lysine and histidine side chains) or of nucleic acids (e.g. cytosine) resulting in a Schiff base formation which then react with another amino group. Repeated treatment after short interval (3 h) caused an enhancement of the crosslinking effect in Chinese hamster V79 but longer intervals induced a decreased effect indicating repair of DNA-adduct in Chinese hamster V79 cells after 24 h (Speit 2007). A repair of DPX was also observed in human blood cells and in human lung, nasal, tracheal and hepatic cell lines after 8-24h in fresh medium depending on the dose level (Cosma 1988, Liu 2006, Schmidt 2007, Speit 2008, Zhao 2009). Repair of DPX was due to both spontaneous hydrolysis and active repair in human lymphocytes and human cell lines (Quievryn 2000). A recent study from Neuss *et al.* (2010b) comes to the conclusion that DPX adducts are the most relevant primary DNA alterations induced by formaldehyde exposure. They are repaired to a similar extent of their induction post-incubation after repeated treatments at low exposure but persistence of DPX has been observed in some studies for exposure to higher formaldehyde concentrations (Schmid 2007). Under test tube conditions, formaldehyde glutathione-conjugate was also observed to link to DNA (Lu 2009).

Positive results on strand break induction were obtained in several studies and in particular on both human lymphocytes and Hela cell lines at low concentration but not at higher concentrations in Liu *et al.* (2006), indicating that at higher concentrations DPX formation may mask the detection of strand breaks in the Comet assay. Using a post-treatment with proteinase K, which abolishes crosslinking effect of formaldehyde, the detection of strand breaks was observed in rat epithelial tracheal cells (Cosma 1988) but not in in Chinese hamster V79 cells (Speit 2007). A complete repair of strand breaks 2 hr after exposure was noted by Cosma et al (1988). It was also observed that the repair of UV-induced single-strand breaks was delayed in presence of formaldehyde (Emri 2004).

Induction of sister chromatid exchanges (SCE) was observed in mammalian cells and in human blood cells in several studies as well as induction of chromosomal aberrations.

Induction of micronuclei was observed in mammalian and human cells. It was detected in Schmid et *al.* (2007) only under specific experimental conditions with indication of an effect on chromosome breaks. However, it was observed under standard conditions in Merck *et al.* (1998), Speit *et al.* (2007) and Speit *et al.* (2000). In Speit *et al.* (2007), repeated treatment with 24-hr intervals did not show an accumulation of micronuclei. However, the meaning of this finding is unclear considering that some micronucleated cells may be discarded by apoptosis.

Formaldehyde has also been shown to induce gene mutations in V79 cells in Grafstrom *et al.* (1993) but not in Merck *et al.* (1998). Positive results are also reported in the MLA assay in Blackburn *et al.* (1991) and in Mackerer *et al.* (1996) and with indications of an effect on chromosomal damage in Speit *et al.* (2002). The effect was not observed in presence of FA deshydrogenase confirming that the genotoxic effect was due to unmetabolised FA (Blackburn 1991).

Altogether, these data indicate that formaldehyde has the potential to damage DNA *in vitro*.

In vivo, at the site of contact, induction of DPX by inhalation was observed in rats in the nasal mucosa and in monkeys in the nasal turbinates and to a lower extent in the respiratory tract (Casanova 1991, Lu 2010, Lu 2011, Moeller 2011). A dose-related increase in DNA damaged as measured by a Comet assay (Sul 2007) was also observed in rats although the detection of such an effect by a Comet assay may be conflicting with the presence of DPX that lead to a decrease in DNA migration. Besides, weak but positive genotoxic effects are observed such as the induction of respectively micronuclei at irritating doses in the gastrointestinal tract via oral route (Migliore 1989) and of chromosomal aberrations in pulmonary cells at the highest dose of 15 ppm by inhalation (Dallas 1992). Compared to the OECD guideline, this latter study display no positive control and fewer cells were analysed than recommended (50 cells/animal instead of 100 in the guideline). However, these limitations were not considered to affect the validity of the study considering that a positive and statistically significant effect was observed at the highest dose in spite of the small number of cells analysed. No increase of micronucleus frequency was found in nasal epithelial cells by inhalation at 20 ppm but in these experimental conditions that induced massive damages in the respiratory epithelium after repeated exposure positive controls also gave a negative result and the study is therefore considered of poor reliability (BASF 2001b). The recent study by Neuss *et al.* (2010c) also found no evidence of DPX in the modified Comet assay and did not reproduce the induction of chromosomal aberrations in its micronucleus assay under experimental conditions comparable to Dallas *et al.* (1992). It should be noted that in Neuss 2010c the positive controls did not give an appropriate response for micronuclei induction. This study was performed according to a non-standard protocol that may explain why the standard positive control used in this assay is not appropriate in this case.

Investigations have shown that formaldehyde induces DNA-protein crosslinks *in vivo* in rats and monkeys with site-specific rate of DPX formation and a non-linear relationship with formaldehyde concentration. A comparative investigation found that induction of SCE and micronuclei induction is parallel to DPX formation *in vitro,* although subsequent induction of gene mutation remains unclear (Merk 1998). Observed DNA damage suggests a mechanism in which DPX prevents replication of DNA (Heck 1999). Inhibition of replication may enhance SCE formation and incomplete repair of DNA might lead to chromosomal aberrations and micronuclei through chromosomal breaks. DPX formation appears therefore as an essential step in the genotoxic events induced by formaldehyde.However, the absence of DPX accumulation following repeated exposure suggests a rapid removal, involving efficient enzymatic removal system or spontaneous dissociation (Casanova 1994). Besides, inhibition of replication by DPX may induce a delay in replication and therefore an inhibitory effect on cell division. Indeed, a J-shaped dose-response in regenerative cell proliferation (RCP) is observed in rats *in vivo* in Monticello et al. (1996) with rates of RCP slightly lower than control at 0.7 and 2 ppm (Conolly 2002, Gaylor 2004). A delay in cell replication at low dose was however not confirmed by the findings of Meng *et al.* (2010) observing a dose-related increase in cell proliferation from 0.7 ppm and significant from 10 ppm.

Cell division is a necessary step in mutation fixation and acceleration in cell cycle do not allow extensive DNA repair before replication. At low dose, the incremental DNA damage may therefore be repaired at non-elevated levels in cell proliferation. This may explain that mutagenic effects are only observed at high doses as confirmed by the observation of chromosomal aberrations *in vivo* at 15 ppm only (Dallas 1992).

Besides, recent studies able to discriminate between DNA-adducts of endogenous or or exogenous origin shows that the level of exogenous DNA-adducts in rat nasal epithelium is of similar order of magnitude than endogenous DNA-adduct level up to 9 ppm but is dramatically increased at 15 ppm (Lu 2011).

In vivo, on somatic cells at distant sites of exposure, no adduct to DNA were detected in different organs of rats at 10 and 15 ppm (Lu 2010, Lu 2011) or in the bone marrow of monkeys up to 6 ppm. Similarly, DPX were not observed in the blood of rats up to 15 ppm (Speit 2009) but DPX were found in the liver cells of mice from 0.8 ppm (Zhao 2009). Im *et al.* (2006) observed DNA damage in the Comet assay in the liver and lymphocytes from 5 ppm. Several studies show that formaldehyde does not induce sister chromatid exchanges, chromosomal aberrations or micronuclei in the rat by inhalation (Speit 2009, Kligerman 1984, Dallas 1992), in mice by IP (Natarajan 1983), oral and i.v. routes (Morita 1997) or in monkeys by inhalation (Moeller 2011). However, Kitaeva *et al.* (1990) observed an increased incidence of chromosomal aberrations in the bone marrow following repeated exposure by inhalation. The reliability of the study was difficult to establish as the complete publication is not available (in Russian) and results are challenged by the negative findings of Dallas *et al.* and of Kligerman *et al.* at similar doses.

In vivo, on germ cells, effects in mammals were investigated in several intraperitoneal (IP) studies that came to inconsistent results. In particular in the recent study by Tang *et al.* (2003), dose related increases in SCE and micronuclei in germ cells were observed. It is consistent with fetal loss observed further to male exposure in Odeigah *et al*. (1997). However, the dose used in this study were much lower than doses inducing chromosomal effects in Tang *et al.* (2003) introducing some inconsistency. However, positive results obtained via intraperitoneal route are not considered as relevant to evaluate the mutagenic potential of formaldehyde on germ cells as normal metabolic pathways are bypassed by IP administration and the test agent is delivered close to the site of contact where it may create a massive irritation. A single study of dominant lethal mutation assay was performed by inhalation (Kitaeva 1990) and provides a weak positive result but as discussed above the reliability of this study cannot be assessed. Liu *et al.* (2009) identified induction of mutations in sperm cells of males exposed to a very high dose of formaldehyde (160 ppm) by inhalation. This study was performed according to a non-standard protocol. Besides, such a high dose is expected to induce excessive toxicity that may interfere with normal physiology of the animal. Besides, inhalation of formaldehyde doesn't modify formaldehyde blood levels in rats, monkeys and humans and due to its high reactivity, its rapid metabolism and detoxification formaldehyde is not expected to reach distant site (Heck 2004) and the biological plausibility for induction of germ cell mutation is therefore weak. Further positive data were obtained in non-mammalian species but their relevance is doubtful.

Human data

In humans at the site of contact, most available studies report an increase in the number of micronuclei in buccal cells in people exposed to formaldehyde. The same effect was observed on nasal mucosa cells except in Suruda *et al.* (1993) and its re-analysis (Titenko-Holland 1996). It is noted that baseline control levels reported in Titenko-Holland *et al.* (1996) were lower than the average micronucleus frequency in a healthy population. Co-exposure to wood dust may have influenced the positive results in nasal mucosa cells in Ballarin et al. (1992) (Speit 2006). Only the study by Speit *et al.* (2007) and Zeller *et al.* (2011) did not detect an increase in micronuclei in the buccal and nasal cells respectively in studies that weres performed under controlled conditions.The exposure and in particular the exposure to peaks may however be lower (maximum of 0.7 ppm with 15 min-peak up to 1 ppm) than in professionally or industrially exposed populations. All the studies were however performed on a small number of subjects, which makes it difficult to interpret. However, these positive results were observed in populations exposed in different settings such as industrial plants (Ballarin 1992 and Ye 2005) and embalming and anatomy/ pathology laboratories (Ying 1997, Burgaz 2001 and 2002), which supports that the positive results are not likely to be due to co-exposures or confounding factors specific to one type of exposure. Altogether indication of a local genotoxic effect of formaldehyde at the site of contact is provided by these studies. It is however noted that standardisation and information on the role of confounding factors is lacking for these protocols (Knasmueller 2011).

In humans at distant sites, many studies have investigated genotoxicity of formaldehyde in peripheral blood lymphocytes and due to the difficulty of collecting sample of bone marrow in humans, no data have therefore investigated genotoxicity directly in the bone marrow. While evidence of chromosomal damages in the Comet assay are provided in Yu *et al.* (2005) and Costa et *al.* (2008), inconsistent results are reported for induction of sister chromatid exchanges (SCE). Both positive and negative findings are also reported in the induction of chromosomal aberrations. However, positive results were consistently reported for micronucleus induction (Suruda 1993, He 1998, Sari-Minodier 2001, Orsière 2006, Viegas 2010), in particular in recent studies showing a positive correlation between the micronuclei frequency and formaldehyde exposure (Yu 2005 and Costa 2008). These positive results were observed mainly in populations exposed in embalming procedures and anatomy/pathology laboratories but also in industrial plants in one study (Ye 2005). Viegas et al. (2010) detected an increase in micronuclei frequency in laboratory workers but not in industrial workers. Mean exposure between both groups was similar but laboratory workers were exposed to 5-fold higher peaks (mean 2.52 ppm). Only two studies did not observe such an effect: no increase in micronuclei was observed in Pala *et al*. (2008) whereas exposure was confirmed by presence of a marker of formaldehyde exposure in the high-exposure group. Even in the high-exposure group the level of formaldehyde was however very low in this study (mean in the high-exposure group of 56.2 µg/m^3 or 0.046 ppm) and may explain the absence of genotoxic effects. Besides, the number of subjects in the high-exposure group was very low (n=7 for micronuclei analysis) and limits the reliability of this result. In Zeller *et al.* (2011), no genotoxicity was detected in peripheral blood of volunteers exposed under controlled conditions. The exposure and in particular the exposure to peaks may however be lower (maximum of 0.7 ppm with 15 min-peak up to 1 ppm) than in professionally or industrially exposed populations.

4.9.4 Comparison with criteria

Annex VI of CLP states for the hazard class germ cell mutagenicity that "the classification in **Category 2** is based on positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:

- Somatic cell mutagenicity tests *in vivo*, in mammals; or
- Other *in vivo* somatic genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assay"

In vivo at the site of contact in somatic cells, positive evidence in mutagenicity tests are available from induction of chromosomal aberrations in rats by inhalation at high dose (Dallas 1992) and of micronuclei in rats in the GI tract by oral route (Migliore 1989).

These positive data are further supported by:

- *in vitro* positive results in numerous genotoxicity and mutagenicity tests
- *in vivo* induction of DNA adducts and DPX at the site of contact
- indications of consistent increases in micronuclei frequency in humans at the site of contact

ECHA guidance to CLP states in section 3.5.2.1.2 that "With the exception of *in vivo* studies proving "site of contact" effects, genotoxicity data from such non-standard *in vivo* studies are not sufficient but may offer supporting information for classification." This implies that tests non standard because they are performed on the site of contact may be sufficient for classification and confirms that effects at the site of contact are relevant for classification.

In vivo at distant sites in somatic cells, indications of consistent increases in micronuclei frequency in humans is available. However, it is not supported by experimental data that report an absence of induction of either genotoxicity or mutagenicity and by inconsistent results for induction of SCE and chromosomal aberrations in humans.

Annex VI of CLP states for the hazard class germ cell mutagenicity that "the classification in **Category 1B** is based on:

- positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
- positive result(s) from *in vivo* somatic cell mutagenicity tests, in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cell. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ

cell *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with genetic material of germ cells; or

- positive results from test showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people. ”

Positive experimental results were obtained on germinal cells *in vivo.* However, they were mainly performed via intra-peritoneal route and are not considered as relevant to evaluate the mutagenic potential of formaldehyde on germ cells as normal metabolic pathways are bypassed by IP administration and the test agent is delivered close to the site of contact where it may create a massive irritation. A single study of dominant lethal mutation assay was performed by inhalation (Kitaeva 1990) and provides a weak positive result but as discussed above the reliability of this study cannot be assessed. Besides, Liu *et al.* (2009) identified induction of mutations in sperm cells of males exposed to a very high dose of formaldehyde by inhalation and such a high dose is expected to induce excessive toxicity that may interfere with normal physiology of the animal. This study was performed according to a non-standard protocol and its significance is unclear in particular on the heritability of the mutations induced.

No data investigating effect on formaldehyde on human germ cells has been located.

Besides, formaldehyde is very quickly metabolised and formaldehyde inhalation does not result in measurable changes in blood levels of formaldehyde in rats and human. In this context, the positive results of *in vitro* studies and the inconsistent results in IP studies are particularly of poor relevance in the assessment of the *in vivo* systemic genotoxic potential via normal routes of exposure. A systemic genotoxic effect on germ cells is therefore unlikely.

Overall, formaldehyde induces mutagenicity *in vivo* on somatic cells at the site of contact but no convincing evidence of an effect on germ cells by a relevant route of exposure is available and the overall database support a classification in category 2.

It is noted that the hazard class for mutagenicity strictly refer to germ cells, but the CLP guidance clearly says in section 3.5.1 (p. 286) that : “It is also warranted that where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens. Classification as a suspected germ cell mutagen may also have implications for potential carcinogenicity classification. This holds true espially for those genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, “site of contact” genotoxicants).”

The genotoxic effect of formaldehyde on somatic cells at the site of contact is therefore relevant to warrant a classification in category 2.

4.9.5 Conclusions on classification and labelling

Based on induction of genotoxic and mutagenic effects of FA on somatic cells at the site of contact, **classification in Category 2 is warranted**.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Table 16: Experimental data on carcinogenicity by oral route

Species	Dose mg/kg/body weight	Durat° of treatm[t]	Observations and Remarks	Ref.
Wistar rats (n=10 to 30 males/group)	Initiation: 100 mg/l MNNG in drinking water and 10% sodium chloride in diet for 8 weeks Promotion: 0.5% formalin equivalent to 0.2% FA in drinking water (equivalent to 2000 mg/l)	32 wk of promo-tion	After initiation with MNNG, significantly increased incidence of adenocarcinoma of the glandular stomach (4/17, 23.5% vs 1/30, 3.3% in the concurrent control group with initiation, p<0.05) and significantly increased incidence of squamous cell papilloma of the forestomach (15/17, 88.2% vs 0/30 in the control group, p<0.01). Without prior initiation, significantly increased incidence of squamous cell papilloma of the forestomach (8/10 rats exposed to FA only and 0/10 in the control group, p<0.01).	Takahashi 1986
Wistar rats (n=50/sex/group) (test substance: paraformaldehyde 95% plus 5% water)	0, 20, 260 or 1900 mg/l FA in drinking water (corresponding to 0, 1.2, 15 and 82 mg/kg/d in males and 0, 1.8, 21 and 109 mg/kg/d in females, respectively)	2 years	No effect on mortality. In the high-dose group: decreased liquid consumption (-40%), decreased food consumption and reduced body weight development; lesions in the forestomach and in the glandular stomach likely due to the corrosive properties of FA; kidney lesions mainly ascribed to dehydration. No other systemic adverse effect. No increased incidence of gastric tumours or tumours at other sites. One generalised histiocytic sarcoma and one myeloid leukaemia were observed in the males at high dose versus none in other male and female groups but were considered incidental. No information is available on historical control data.	Til, 1989

Wistar rats (n=20/sex /group) (test substance: crystalline para-formaldehyde, purity 80%)	0, 0.02, 0.1 or 0.5% FA in drinking-water (approx. 0, 10, 50 or 250 mg/kg/d)	2 year	In the high-dose group: significant decreases in body weight and food and water intake; 100% mortality by 24 months; erosions and/or ulcers in the forestomach and glandular stomach; squamous cell hyperplasia with or without hyperkeratosis in the forestomach. A few signs of irritation of the GI tract in the 0.10% group. No increase of local or systemic tumour incidence compared to controls (incidence of individual tumours not given in the publication).	Tobe 1989
Sprague-Dawley rats (n=50/sex) (7-wk old) (test substance: formaldehyde stabilised with methanol 0.3%, impurities: iron 0.6 mg/l, lead 0.1 mg/l, sulphur <5.0 mg/l, chlorine <5.0 mg/l)	0, 10, 50, 100, 500, 1000 or 1500 mg/l FA with 0.3% methanol in drinking water (approx. 0, 1.28, 6.44, 12.8, 64.4, 128 and 192 mg/kg/d in males and 0, 1.45, 7.24, 14.5, 72.4, 145 and 217 mg/kg/d in females, respectively) + additional methanol control group: 15 mg/l methanol	24 mo (+ lifetime obs.)	No effect on survival or body weight Increased incidence of all hemolymphoreticular neoplasias in the treated group: 22% and 14% in the males and females at highest dose compared to 4% and 3% in the untreated control males and females and 10% and 6% in the methanol males and females, respectively. No analysis performed by subtype. Occasional increased incidence of gastro-intestinal tumours but not dose-related. At the highest dose 6% of females had intestine leiomyomas vs none in controls (historical data: 0.04%) and 4% of males had intestine leiomyosarcomas vs none in controls (historical data: 0.04%). No statistical analysis provided.	Soffritti 1989
Sprague-Dawley rats (n=50/sex) (7-wk	0, 10, 50, 100, 500, 1000 or 1500 mg/l FA with 0.3% methanol in drinking water (approx. 0, 1.28, 6.44, 12.8, 64.4, 128 and 192 mg/kg/d in males and 0,	24 mo (+ lifetime obs.)	Decrease in water intake in high-dose males and females treated over 500 mg/l. No difference in food consumption, body weight and survival. Increase in total malignant tumour incidence in males and females at 1500 mg/l, in males at 500 mg/l and in females at 1000 and 100 mg/l.	Soffritti 2002

old) (test substance: aqueous solution of formaldehyde at 30±0.2% stabilised with methanol 0.3%, impurities: iron 0.6 mg/l, lead 0.1 mg/l, sulphur <5.0 mg/l, chlorine <5.0 mg/l)	1.45, 7.24, 14.5, 72.4, 145 and 217 mg/kg/d in females, respectively) + additional methanol control group: 15 mg/l methanol		Statistically significant only in high-dose males when compared to the methanol group. Increase (not dose-related) in malignant mammary glands tumours incidence in females, which is significant (p<0.05) at high dose when all mammary tumours are pooled (adenocarcinoma rates: 11%, 4%, 8%, 16%, 6%, 18% and 22% in rats treated with 0, 10, 50, 100, 500, 1000 or 1500 mg/l, respectively). Not statistically significant when compared to the methanol group (14%). Sporadic cases of rare stomach and intestine tumours (0% in untreated and methanol controls): at the highest dose, 2 females (4%) and 1 male (2%) had glandular stomach adenocarcinoma, 3 females (6%) had intestine leiomyoma, 3 males (6%) intestine adenocarcinoma and 2 intestine leiomyosarcoma (4%); 1 male treated with 1000 mg/l had stomach leiomyosarcoma; at the highest dose). Increase (not dose-related) in testicular interstitial cell adenomas: 10%, 6%, 12%, 12%, 20%, 24% (p<0.05) and 18% in male rats treated with 0, 10, 50, 100, 500, 1000 or 1500 mg/l, respectively (6% in methanol group). No malignant tumours. Increase in incidence of hemolymphoreticular neoplasias (8%, 8%, 20%, 26%, 24%, 22% and 46% in males and 7%, 10%, 14%, 16%, 14%, 22% and 20% in females treated with 0, 10, 50, 100, 500, 1000 or 1500 mg/l, respectively). Incidence of hemolymphoreticular neoplasia was also increased in the methanol group (20% in males and 10% in females). Compared to the methanol group, only incidence in the high dose males was significantly increased (p<0.01).	

4.10.1.2 Carcinogenicity: inhalation

Table 17: Experimental data on carcinogenicity by inhalation

Species	Conc. mg/ m^3	Expo. time (h/day)	Durat° of treatm^t	Observations and Remarks	Ref.
F-344 rats (n=120/sex/group) (test substance: paraformaldéhyde heated to obtain FA gas, with no significant levels of contamination or pyrolysis products. No metal > 0.01%)	0, 2.4, 6.7 or 17.2 mg/ m^3 (0, 2.0, 5.6 or 14.3 ppm)	6h/d 5d/wk (whole -body)	24 mo (+ 6 mo obs.)	Gross pathological examinations were performed on all animals. Tissue masses and multiple sections of nasal turbinates were observed histologically. Male and female rats exhibited an increased mortality from 12 months onwards in the 17.2 mg/ m^3 exposure group and from 17 months onwards in the males exposed to 6.7 mg/ m^3. Rats in the 17.2 mg/ m^3 exposure group were dyspneic and emaciated. Rhinitis, epithelial dysplasia, and squamous metaplasia were observed in all treated groups and confined to the nasal cavity and proximal trachea. Alterations of the epithelium were initially restricted to the ventral portion of the nasal septum and the distal tips of the nasoturbinates and maxilloturbinates. As the study progressed, the distribution and severity of lesions within the nasal cavity increased in all exposure groups. Nasal polyploid adenoma: 1/232, 8/236, 6/235 and 5/232 rats (not significant) exposed to 0, 2.4, 6.7 or 17.2 mg/ m^3, respectively. Nasal squamous cell carcinoma: 0/232, 0/236, 2/225 (1%, not significant) and 103/232 (44%; 51/117 males and 52/115 females, $p<0.001$) in rats exposed to 0, 2.4, 6.7 and 17.2 mg/ m^3, respectively. Additional nasal cavity tumours (carcinoma, undifferentiated carcinoma or sarcoma or carcinosarcoma) identified in 5/232 animals of the high dose group. Nasal neoplastic lesions originated in the anterior portion of the nasal cavity and in few instances extended into the ethmoturbinates.	Kerns 1983 (study report: Battelle 1981)

				Leukaemia in 11/120 (9%) control females and in 7/120 (6%) in high-dose females (not significant). Leukaemia in 11/110 (9%) control males and in 5/120 (4%) high-dose males (not significant).	
Sprague-Dawley rats (n=16 females) (Test substance purity not available)	0 or 14.4 (0 or 12 ppm) (with or without coexposure to 25 mg/m^3 of wood dust)	6h/d 5d/wk	24 mo	One well differentiated squamous cell carcinoma in the FA group (not significant). Squamous cell metaplasia (10/16 compared to 0/15 in controls) was found significantly more often among the FA-exposed rats but squamous cell metaplasia with dysplasia was most frequently observed in the group exposed to both FA and wood dust.	Holmström 1989
F-344 rats (n=90-150 male/group) (test substance: paraformaldéhyde heated to obtain FA gas)	0, 0.8, 2.4, 7.2, 12 or 18 (0, 0.7, 2, 6, 10 or 15 ppm)	6h/d 5d/wk (whole-body)	24 mo	Significant decrease in survival in the high-dose group relative to that of control (18.8% vs 35.7%, $p<0.001$) Histopathology was focused on the nasal cavity. Histopathological changes and increased epithelial cell proliferation in the nasal cavity (transitional and respiratory epithelium). NOAEL: 2.4 mg/m^3 Nasal squamous cell carcinoma: 0/90, 0/90, 0/96, 1/90 (1%), 20/90 (22%) and 69/147 (47%) rats exposed to 0, 0.8, 2.4, 7.2, 12 and 18 mg/m^3, respectively. Majority of tumours were located in the lateral meatus and some on the nasal septum. Nasal polyploid adenomas: 0/90, 0/90, 0/96, 0/90, 5/90 (5.6%) and 14/147 (9.5%) rats exposed to 0, 0.8, 2.4, 7.2, 12 and 18 mg/m^3, respectively. Nasal rhabdomyosarcomas: 0/90, 0/90, 0/96, 0/90, 1/90 (1%) and 1/147 (0.7%) rats exposed to 0, 0.8, 2.4, 7.2, 12 and 18 mg/m^3, respectively. Nasal adenocarcinomas: 0/90, 0/90, 0/96, 0/90, 1/90 (1%) and 1/147 (0.7%) rats exposed to 0, 0.8, 2.4, 7.2, 12 and 18 mg/m^3, respectively. Increase in cell proliferation (measured by labelling index) in the 10- and 15-ppm groups. Regional tumour rate is strongly associated with labelling index multiplied by local cell	Monticello 1996

				population (R^2=0.88). Average cell division rate constant were calculated based on these data in Conolly 2002 and showed a J-shape with significantly increased regenerative cell proliferation (RCP) in rats from 6 ppm and slightly lower RCP at 0.7 and 2 ppm although not significant. Statistical analyses for each site of the nasal mucosa were performed in Gaylor 2004. At the posterior medial septum, reduction of the labelling index in the 2 ppm group was statistically signicant.In this study, use of different statistical model to the dose-response curve suggests a J-shape curve rather than a linear curve.	
Wistar rats (n=45 males/group) (test substance purity not given)	0, 12 or 24 (0, 10 or 20 ppm)	6h/d 5d/wk (whole-body)	4, 8 or 13 wk (+up to 126 wk obs.)	All animal were examined for gross pathological changes. Light microscopic examination was restricted to the nose. Rats exposed to 20 ppm had significantly lower body weights than controls during the exposure periods. Despite recovery periods, rats exposed to 20 ppm for 4, 8 or 13 weeks exhibited rhinitis focal hyperplasia and stratified squamous metaplasia of the respiratory epithelium (statistically significant). Similar but less severe lesions were observed in rats exposed to 10 ppm and were significant only for an exposure of 13 weeks. Focal replacement of olfactory epithelium by modified epithelium was also observed in rats exposed at 20 ppm for 8 or 13 weeks. Squamous cell carcinomas in rats exposed for 4 weeks: 0/44, 0/44 and 1/45 at 0, 10 and 20 ppm respectively. Squamous cell carcinomas in rats exposed for 8 weeks: 2/45, 1/44 and 1/43 at 0, 10 and 20 ppm respectively. Squamous cell carcinomas in rats exposed for 13 weeks: 0/45, 1/44 and 3/44 at 0, 10 and 20 ppm respectively. At the highest dose, 1 cystic squamous cell carcinoma, 1 carcinoma in situ and 1 amenoblastoma were also observed in the nasal cavity (none in controls).	Feron 1998
Wistar	0, 0.12, 1.2 or	6h/d	28 mo	All animal were examined for gross pathological changes. Light microscopic	Wouterse

rats (n=60 males with damaged and 30 with undamaged nose) (test substance purity not given)	11.8 (0, 0.1, 1 or 9.8 ppm)	5d/wk (whole-body)		examination of the nose was performed. Degenerative, inflammatory and hyperplastic changes of the nasal respiratory and olfactory mucosa in rats with intact nose at the highest dose. Nasal electrocoagulation increased the incidences of FA-induced rhinitis, hyper- and metaplasia of the respiratory epithelium, and degeneration and hyper- and metaplasia of the olfactory epithelium. Squamous metaplasia and rhinitis were present in all exposed groups with damaged nose. NOAEL: 1.2 mg/m^3 Increased incidence of nasal squamous cell carcinomas at the highest dose in rats with damaged nose (15/58: 26% vs 1/54 in controls) but not in rats with intact nose (1 SCC equivalent to 3.5-4% in each treated group, 0/26 in the controls). Exposure to FA for 3 months followed by a 25-month observation period did not induce a significant increase in nasal tumours (0/26, 0/30, 0/29 and 1/26 in animals with intact nose at 0, 0.12, 1.2 and 12 mg/ m^3 respectively and 0/57, 2/57, 2/53 and 1/54 in animals with damaged nose at 0, 0.12, 1.2 and 12 mg/ m^3 respectively).	n 1989
F-344 rats (n=32 males/ group with 5 sacrificed at week 12, 18 and 24) (test substance formalin with 37% FA and 10% methanol)	0, 0.36, 2.4 or 18 (0, 0.3, 2 or 15 ppm) Controls exposed to 4.2 ppm of methanol (equivalent to the methanol exposure in the 15 ppm FA group)	6h/d 5d/wk (whole-body)	28 mo	Autopsies were performed and histological examinations were performed on main organs, sections of the nasal turbinates and any gross lesions. Histopathological changes in the nasal cavity in all treated groups including hyperkeratosis in 1/32 and 26/32 rats at the two highest doses. Hyperplasia with squamous cell metaplasia in 0/32, 0/32, 4/32 and 7/32 at 0, 0.36, 2.4 and 18 mg/ m^3, respectively. No microscopic lesions in the organs other than the nasal cavity. Significant decrease in food consumption and body weight, significant increase in mortality, reduced triglyceride levels and liver weights at the highest dose. LOAEL: 0.36 mg/ m^3 Nasal squamous cell carcinoma: 0/32, 0/32, 0/32 and 13/32 (41%) rats at 0, 0.36, 2.4 and 18 mg/ m^3, respectively. 3 squamous cell papillomas (9%) and 1	Kamata 1997 (=Tobe 1985)

				sarcoma (3%) in animals of the high dose group (none of the controls). Leukaemia were observed in 7/32, 2/32, 5/32 and 0/32 animals in the 0, 0.3, 2 and 15 ppm groups, respectively and was not increased with treatment.	
Sprague-Dawley rats (n=100 males/group)	0 or 18 (0 or 14.8 ppm)	6h/d 5d/wk (whole body)	For life	Complete necropsy was performed on each animal with particular attention to the respiratory tract. A substantially higher mortality was seen in FA exposed animals from around week 80 but not after week 112. Histopathological changes were observed in the nasal cavity including squamous metaplasia (60/100 in the exposed group vs 5/99 in controls). Hyperplasia and squamous metaplasia were also observed in the larynx and trachea. Nasal squamous cell carcinomas: 38/100 in the exposed group, 0/99 in the control group (p=0.01). Mixed nasal carcinomas: 1/100 in the exposed group, 0/99 in the control group. Nasal fibrosarcomas: 1/100 in the exposed group, 0/99 in the control group. Nasal polyps or papillomas: 10/100 in the exposed group, 0/99 in the control group (p=0.01). No difference in the tumour incidence in organs outside the respiratory tract between exposed and control groups. It includes 3 malignant lymphomas in the FA exposed group vs 2 in controls.	Sellakumar 1985 (preliminary results in Albert 1982)

Mice (n=120/sex) (test substance: paraformaldéhyde heated to obtain FA gas, with no significant levels of contamination or pyrolysis products. No metal > 0.01%)	0, 2.4, 6.7 or 17.2 (0, 2.0, 5.6 or 14.3 ppm)	6h/d 5d/wk	24 mo (+ 6 mo obs.)	Reduced body weight at 14.3 ppm in females. No significant reduction of survival. Rhinitis, epithelial dysplasia, and squamous metaplasia were observed in the upper respiratory tract in the two highest dose groups. NOAEL: 2.4 mg/ m^3 Nasal squamous cell carcinoma: 2/108 male mice (2%) at the high dose (not significant) vs none in the other groups. Lymphoma in 19/121 (16%) control females and in 27/121 (22%) in high-dose females (not significant). No lymphoma in male mice.	Kerns 1983 (study report: Battelle 1981)
Syrian golden hamsters (1^{st} exp: n=88 exposed males and 132 controls) (2^{nd} exp: n=50 males) (test substance: paraformaldéhyde heated; purity not given)	1^{st} exp: 0 or 12 (0 or 10 ppm) 2^{nd} exp: 0 or 36 (0 or 30 ppm)	1^{st} exp: 5h/d 5d/wk 2^{nd} exp: 5h/d 1d/wk (whole-body)	Lifetime	1^{st} exp: All major tissues were preserved at necropsy. Decrease in survival time was observed in the treated animals (statistical significance not known). No tumours were observed in the respiratory tract. Minimal hyperplasia and metaplasia in the nasal epithelium at 10 ppm (5% of exposed hamster vs none in the controls). 2^{nd} exp: At death, only the respiratory tract was preserved. No effect was observed on survival and no tumours in the respiratory tract in the FA treated group (30 ppm). Increased incidence of tracheal tumours in animals treated with diethylnitrosamine (DEN) + FA compared to animals treated with DEN alone.	Dalbey 1982

4.10.1.3 Carcinogenicity: dermal

Table 18: Experimental data on carcinogenicity by dermal route

Species	Dose mg/kg/body weight	Expo-sure time	Durat° of treatm[t]	Observations and Remarks	Ref.
Sencar mice (n=30 females/group) (test substance purity not given)	Initiation with DMBA or 3.7% FA in acetone. Promotion with 3.7% FA in acetone	Initiation once Promotion once a week	48 wk	No papillomas in the group exposed to FA as initiator and promoter. When FA was used as an initiator, no difference with acetone controls was seen. The author concluded on a very weak promoting potential to be confirmed.	Spangler 1983 (limited report of the results)
CD-1 mice (n=30 females/ group) (test substance: FA prepared from 96.8% pure paraformaldehyde) Solvent: 50:50 acetone:water	Initiation study: initiation with 10% FA in and promotion with acetone or phorbol myristate acetate (TPA). Promotion study: initiation with BaP and promotion TPA, acetone , 0.1, 0.5 or 1% FA. Initiation and promotion: initiation with 10 % FA and promotion with 1% FA.	Initiation once Promotion 3 times a week	26 wk (+26 wk of recove-ry)	Mice were examined for skin tumours only. Malignant skin tumours were observed only in the group initiated with BaP and promoted with TPA (32% of animals). None was reported in groups treated with FA as initiator, promoter ar initiator and promoter. The incidence of benign skin tumours (keratoacanthoma or squamous papilloma) in FA-treated groups (initiation/promotion) was: - FA/TPA: 10% - FA/acetone: 0% - FA/FA: 0% - BaP / 0.1% FA: 20% - BaP / 0.5% FA: 7% - BaP / 1% FA: 0% No statistical difference with controls was observed. In the BaP/TPA positive control group, the incidence of benign tumours was 52%.	Krivanek 1983

Oslo hairless mice (n=16/sex) (test substance: formalin of technical grade with 40% FA)	Treatment with 200 µg of 1 or 10% FA in water One group was pre-treated with DMBA and treated with FA 10% twice a week starting 9 weeks after. No control group	Twice a week	60 wk	All animals exposed to 10% FA were autopsied and all organs were inspected. Slight epidermal hyperplasia, a few skin ulcers and two small lung nonspecific granulomas were observed in the 10% group. No tumours in the groups treated with FA alone. In the DMBA/FA group, final tumour rate was not significantly different from the final tumour rate after DMBA alone, but the time of appearance of the first tumour and the mean latency time was significantly reduced (p=0.01)	Iversen 1988

4.10.2 Human information

4.10.2.1 Industrial cohort studies

Table 19: Industrial cohort studies

Cohort description	Estimation of exposure	Cancer site	Risk estimate	Observations and remarks	Ref

NCI cohort 10 US formaldehyde production or use facilities n=25619 workers of one of the plant before 1966 Follow-up through 2004 Reference: sex-, ethnicity-, age- and calendar year-specific US mortality rate	Job history and assessment of peak and average exposure and frequency by an industrial hygienist. Median TWA: 0.3 ppm (range: 0.01-4.3) 17% were never exposed to formaldehyde 15% had average exposure >1 ppm and 24% peak exposure >4 ppm.	All cancer mortality <u>Lymphohaematopoietic malignancies:</u> Non-Hodgkin's lymphomas: Hodgkin's disease: Multiple myeloma: Leukaemia: Lymphatic leukaemia: Myeloid leukaemia	Unexposed : SMR=0.93 (95% CI: 0.84-1.03) Exposed : **SMR=1.07 (95% CI: 1.03-1.11)** Unexposed : SMR=0.86 (95% CI: 0.61-1.21) Exposed : SMR=0.94 (95% CI: 0.84-1.06) Unexposed : SMR=0.86 (95% CI: 0.49-1.52) Exposed : SMR=0.85 (95% CI: 0.70-1.05) Unexposed : SMR=0.70 (95% CI: 0.17-2.80) Exposed : SMR=1.42 (95% CI: 0.96-2.10) Unexposed : SMR=1.78 (95% CI: 0.99-3.22) Exposed : SMR=0.94 (95% CI: 0.71-1.25) Unexposed : SMR=0.48 (95% CI: 0.23-1.01) Exposed : SMR=1.02 (95% CI: 0.85-1.22) Unexposed : SMR=0.26 (95% CI: 0.04-1.82) Exposed : SMR=1.15 (95% CI: 0.83-1.59) Unexposed : SMR=0.65 (95% CI: 0.25-1.74) Exposed : SMR=0.90 (95% CI: 0.67-1.21) RR for myeloid leukaemia for peak exposure 0 ppm: 0.82 (95% CI:0.25-2.67) > 0-2.0 ppm: 1.0 2.0-4.0 ppm: 1.30 (95% CI:0.58-2.92) ≥4.0 ppm: 1.78 (95% CI: 0.87-3.64) RR for myeloid leukaemia for average intensity exposure 0 ppm: 0.70 (95% CI:0.23-2.16) > 0-0.5 ppm: 1.0 0.5-1.0 ppm: 1.21 (95% CI:0.56-2.62) ≥1.0 ppm: 1.61 (95% CI: 0.76-3.39) RR for myeloid leukaemia for cumulative exposure 0 ppm-year: 0.61 (95% CI:0.20-1.91) > 0-1.5 ppm-year: 1.0 1.5-5.5 ppm-year: 0.82 (95% CI:0.36-1.83) ≥5.5 ppm-year: 1.02 (95% CI: 0.48-2.16)	Relative risk for lymphohaematopoietic malignancies (p trend =0.004), leukaemia (p trend = 0.02), myeloid leukaemia (p trend = 0.07) and Hodgkin lymphoma (p trend =0.004) increased with peak exposure compared with the lowest exposure category. For average intensity of exposure, there was a statistically non significant increase for myeloid leukaemia (p trend=0.40) and Hodgkin lymphoma (p trend =0.03). No association was observed for cumulative exposure except weak association for Hodgkin lymphoma (p trend=0.06). Controlling for duration of exposure to 11 potential confounders, excluding individuals with potential benzene exposure and adjusting for plant did not substantially change results. Highest risk for myeloid leukaemia occurred before 1980 for peak exposure but trend tests attained statistical significance in 1990 only. After the mid1990s, the risk for myeloid leukaemia declined.	Beane Freeman 2009

NCI cohort 10 US formaldehyde production or use facilities n=25619 workers of one of the plant before 1966 Follow-up through 1994 Reference: sex-, ethnicity-, age- and calendar year-specific US mortality rate	Job history and assessment of peak and average exposure and frequency by an industrial hygienist. Median TWA: 0.5 ppm (range: 0-4.3) 2.6% had average exposure >2 ppm and 14.3% peak exposure>4 ppm.	All cancer mortality Lymphohaematopoietic malignancies: Non-Hodgkin's lymphomas: Hodgkin's disease: Multiple myeloma: Leukaemia: Solid cancers: Buccal cavity Nasopharynx Pancreas Digestive system Resp. system Nose and nasal cavity Larynx Lung Bone Brain and CNS Breast Prostate	SMR=0.90 (95% CI: 0.86-0.94) SMR=0.80 (95% CI: 0.69-0.94) SMR=0.61 (95% CI: 0.46-0.83) SMR=1.26 (95% CI: 0.81-1.95) SMR=0.88 (95% CI: 0.61-1.28) SMR=0.85 (95% CI: 0.67-1.09) SMR=0.91 (95% CI: 0.87-0.96) SMR=1.01 (95% CI: 0.77-1.34) **SMR=2.10 (95% CI: 1.05-4.21)** SMR=0.83 (95% CI: 0.67-1.04) SMR=0.89 (95% CI: 0.80-0.97) SMR=0.97 (95% CI: 0.90-1.04) SMR=1.19 (95% CI: 0.38-3.68) SMR=0.95 (95% CI: 0.63-1.43) SMR=0.97 (95% CI: 0.90-1.05) SMR=1.57 (95% CI: 0.75-3.29) SMR=0.81 (95% CI: 0.58-1.11) SMR=0.59 (95% CI: 0.38-0.92) SMR=0.90 (95% CI: 0.75-1.06) RR for myeloid leukaemia for peak exposure 0 ppm: 0.67 (95% CI:0.12-3.61) > 0-2.0 ppm: 1.0 2.0-4.0 ppm: 2.43 (95% CI:0.81-7.25) **≥4.0 ppm: 3.46 (95% CI:1.27-9.43)** RR for myeloid leukaemia for average intensity exposure 0 ppm: 0.41 (95% CI:0.08-1.95) > 0-0.5 ppm: 1.0 0.5-1.0 ppm: 1.15 (95% CI:0.41-3.23)	Relative risk for leukaemia and particularly myeloid leukaemia increased with peak and average intensity of exposure but not with cumulative exposure or duration. Excess of ML reached statistical significance in the higher groups when analyses by peak or average intensity exposure. For Hodgkin's disease, a positive trend was found with increasing peak, average intensity and cumulative exposure but not with duration. No substantial difference after exclusion of the 586 subjects exposed to benzene. No significant positive trend for any solid cancer with increasing average intensity or duration of exposure. Relative risk for nasopharynx cancer increased with peak exposure. Relative risk for nasopharynx and bone cancers increased with cumulative exposure. 2 nasopharynx cancer deaths occurred in non-exposed workers and 8 among exposed workers. All exposed cases had maximum peak exposure > 4 ppm. All were also exposed to particulates. Nasopharyngeal relative risk was declined after adjustment for melanine exposure but trends were still significant for peak, cumulative and duration of exposure.	Hauptmann 2003 and 2004

			RR for myeloid leukaemia for cumulative exposure 0 ppm-year: 0.32 (95% CI:0.07-1.51) > 0-1.5 ppm-year: 1.0 1.5-5.5 ppm-year: 0.57 (95% CI:0.19-1.73) ≥5.5 ppm-year: 1.02 (95% CI: 0.40-2.55) RR for myeloid leukaemia for duration of exposure 0 year: 0.34 (95% CI:0.07-1.67) 0.1-4.9 years: 1.0 5-14.9 years: 0.49 (95% CI:0.14-1.73) 15 years: 1.35 (95% CI: 0.56-3.24)		
Reevaluation of NCI cohort for leukaemia : alternative categorization of exposure and US and regional external rate-based SMR		Leukaemia	Similar RR estimates to those reported by Hauptmann 2003 but lower SMR (external comparisons).	Longer duration of work in the highest peak exposure category did not result in higher risks. SMRs increased with increasing peak and average intensity of exposure for all leukaemia and myeloid leukaemia.	Marsh 2004

Reevaluation of NCI cohort for nasopharyngeal cancer: alternative categorization of exposure and US and regional external rate-based SMR; separate analysis of plants.	Average intensity of exposure was higher in plant 2 (2.8 ppm) and plant 1 (1.0 ppm) compared to the other plants (≤0.5 ppm).	Nasopharyngeal cancers	Six of the 10 NPC cases occurred in plant 1 in exposed workers. The 4 other deaths occurred individually in 4 other plants, 2 in exposed workers and 2 in unexposed workers. All workers, based on US rates: **SMR plant 1 : 6.62 (95% CI: 2.43-14.40)** SMR plants 2-10: 0.96 (95% CI: 0.26-2.45) All workers, based on regional rates: **SMR plant 1 : 7.39 (95% CI: 2.71-16.08)** SMR plants 2-10: 0.98 (95% CI: 0.27-2.51) Exposed workers, based on US rates: **SMR plant 1 : 9.13 (95% CI: 3.35-19.88)** SMR plants 2-10: 0.64 (95% CI: 0.08-2.30) Exposed workers, based on regional rates: **SMR plant 1 : 10.32 (95% CI: 3.79-22.47)** SMR plants 2-10: 0.65 (95% CI: 0.08-2.33)	In plant 1, NPC incidence increases with peak and average exposure but not with cumulative exposure or duration. All cases are in the highest peak exposure category. In plants 2-10, 2 NPC cases are among unexposed workers and 2 in workers of the highest peak exposure category. Using local comparisons and alternate exposure categorisation: - analysing all plants together, a statistical increased SMR was confirmed for the highest categories of peak, average intensity and cumulative exposure but not for duration of exposure - analysing plant 1 only, a statistical increased SMR was identified for the highest categories of peak and average intensity but not for cumulative exposure or duration of exposure - analysing plant 2-10, only not statistical increased SMR were identified for the highest categories of peak, average intensity, cumulative exposure or duration of exposure.	Marsh 2005
Reevaluation of NCI cohort for nasopharyngeal cancer: appropriateness of model specification and exploration of instability of the risk estimates in relation to highest peak exposure.		Nasopharyngeal cancers	Internal rate-based ratios by peak FA exposure without control for plant group: Unexposed: RR: 1.0 0-1.9 ppm-years: 0.20 (95% CI: ∞-2.74) 2.0-3.9 ppm-years: 0.24 (95% CI: ∞-3.27) ≥4.0 ppm-years: 1.80 (95% CI: 0.28-20.81) Adjusted for plant group: Unexposed: RR: 1.0 0-1.9 ppm-years: 0.28 (95% CI: ∞-3.87) 2.0-3.9 ppm-years: 0.21 (95% CI: ∞-2.89) ≥4.0 ppm-years: 1.41 (95% CI: 0.19-17.62)	Reanalysis found evidence of an interaction effect of continuous peak formaldehyde exposure and plant group indicator. Sensitivity analysis demonstrates that taking only one additional death produced a high degree of variation of risk estimates.	Marsh 2007b

Plant 1 of NCI cohort (Wallingford plastics producing plant) n=7345 workers at risk between 1945 and 2003 Follow-up through 2003 Reference: sex-, ethnicity-, age- and calendar year-standard US mortality rate and local county rate.	Job history and sporadic sampling data between 1965 and 1987. Median average intensity of exposure: 0.138 ppm in the 5649 exposed workers.	Pharynx - Nasopharynx Sinonasal Nose and nasal cavity	**US SMR: 2.38 (95%CI: 1.51-3.57)** **Local SMR: 2.10 (95% CI: 1.33-3.16)** **US SMR: 4.34 (95%CI: 1.74-8.94)** **Local SMR: 4.43 (95% CI: 1.78-9.13)** US SMR: 2.66 (95%CI: 0.55-7.77) Local SMR: 2.64 (95% CI: 0.54-7.71) No case observed	Only 4 NPC out of 7 observed were exposed to FA for more than 1 year. A nested case control studies was also performed on this plant and results are reported p 102 of the present CLH report.	Marsh 2007a
Plant 1 of NCI cohort (Wallingford plastics producing plant) n=7328 workers employed between 1941 and 1998 Follow-up through 1998 Reference: sex-, ethnicity-, age- and calendar year-standard US mortality rate and local county rate.	Job history and sporadic sampling data between 1965 and 1987. Median average intensity of exposure: 0.138 ppm in the 5665 exposed workers.	Pharynx - Nasopharynx Sinonasal Nose and nasal cavity	**US SMR: 2.63 (95%CI: 1.65-3.98)** **Local SMR: 2.23 (95% CI: 1.40-3.38)** **US SMR: 4.94 (95%CI: 1.99-10.19)** **Local SMR: 5.00 (95% CI: 2.01-10.30)** US SMR: 3.10 (95%CI: 0.64-9.07) Local SMR: 3.06 (95% CI: 0.63-8.93) No case observed	Only 4 NPC out of 7 observed were exposed to FA for more than 1 year. Limited evidence of an association with increasing duration of exposure, cumulative exposure or duration of employment in jobs with FA exposures > 0.2 or 0.7 ppm.	Marsh 2002

British chemical workers cohort 6 British chemical factory using or producing formaldehyde n=14014 men employed after 1937 Follow-up through December 2000 Reference: national rates of mortality for England and Wales adjusted for local geographical variations	Job-exposure matrix was used and subjects were qualified into one of the 5 exposure categories: background (estimated TWA <0.1 ppm), low (estimated TWA 0.1-0.5 ppm), moderate (estimated TWA 0.6-2.0 ppm), high (estimated TWA >2 ppm) or unknown.	All cancer mortality Stomach cancer Lung cancer Pharynx cancer Nose and nasal sinuses cancer Larynx cancer Tongue cancer Mouth cancer Pancreas cancer Rectum cancer Brain and nervous system Leukaemia	**SMR=1.10 (95% CI: 1.04-1.16)** **SMR=1.31 (95% CI: 1.11-1.54)** **SMR=1.53 (95% CI: 1.17-1.95) at high exposure** **SMR=1.22 (95% CI: 1.12-1.32)** **SMR=1.58 (95% CI: 1.40-1.78) at high exposure** **Positive trend with exposure categories (p<0.01)** SMR=1.55 (95% CI: 0.87-2.56) SMR=1.91 (95% CI: 0.70-4.17) at high exposure SMR=0.87 (95% CI: 0.11-3.14) SMR=0.0 (95% CI: 0.0-4.64) at high exposure SMR=1.07 (95% CI: 0.58-1.79) SMR=1.56 (95% CI: 0.63-3.22) at high exposure SMR=0.84 (95% CI: 0.23-2.14) SMR=1.91 (95% CI: 0.39-5.58) at high exposure SMR=1.28 (95% CI: 0.47-2.78) SMR=1.32 (95% CI: 0.16-4.75) at high exposure SMR=0.99 (95% CI: 0.75-1.28) SMR=0.91 (95% CI: 0.54-1.44) at high exposure SMR=1.21 (95% CI: 0.94-1.52) SMR=0.85 (95% CI: 0.57-1.21) SMR=0.63 (95% CI: 0.25-1.29) at high exposure SMR=0.91 (95% CI: 0.62-1.29) SMR=0.71 (95% CI: 0.31-1.39) at high exposure	Excess of stomach cancer deaths in men with high exposure was no more significant after local adjustments: SMR: 1.28 (95% CI: 0.98-1.64). No significant trend with exposure category. Excess of lung cancer deaths in men with high exposure remained significant after local adjustments: SMR: 1.28 (95% CI: 1.13-1.44) but with an inverse trend with the number of years worked in high exposure jobs (p=0.13). Pharynx cancers: include only one death (low category of exposure) from nasopharynx cancer (2.0 expected). No data on smoking habits. No excess of deaths from prostate, breast, oesophagus or thyroïd cancers.	Coggon 2003 (and further correspond -dance on the study in Greenberg 2004)

NIOSH garment cohort 3 garment manufacturing facilities in the USA n=11039 workers employed for at least 3 months after first formaldehyde introduction into process Follow-up through 1998 Reference: US and local states age, gender, race and cause specific mortality rates comparisons	Mean TWA ranged from 0.09 to 0.20 ppm across departments in 1981 and 1984 (mean concentration: 0.15 ppm) Formaldehyde levels were essentially constant without substantial peak exposure. Exposure was believed to be substantially higher in earlier years.	All cancer mortality Buccal+pharyngeal: Buccal cavity Pharynx Stomach Pancreas All respiratory: Larynx Trachea/bronchus/lung Other resp. Brain Prostate Thyroïd All lymphohaematopoietic: Lymphosarcoma and reticulosarcoma: Hodgkin's disease Leukaemia Myeloid leukaemia Acute ML Chronic ML Other ML Lymphocytic leuk. Other/unspecified leuk.	SMR=0.89 (95% CI: 0.82-0.97) SMR=0.79 (95% CI: 0.34-1.55) SMR=1.33 (95% CI: 0.36-3.41) SMR=0.64 (95% CI: 0.13-1.86) SMR=0.80 (95% CI: 0.42-1.36) SMR=0.81 (95% CI: 0.53-1.18) SMR=0.98 (95% CI: 0.83-1.14) SMR=0.88 (95% CI: 0.18-2.59) SMR=0.98 (95% CI: 0.82-1.15) SMR=1.21 (95% CI: 0.15-4.37) SMR=1.09 (95% CI: 0.66-1.71) SMR=1.58 (95% CI: 0.79-2.83) SMR=1.16 (95% CI: 0.14-4.18) SMR=0.97 (95% CI: 0.74-1.26) SMR=0.85 (95% CI: 0.28-1.99) SMR=0.55 (95% CI: 0.07-1.98) SMR=1.09 (95% CI: 0.70-1.62) SMR=1.44 (95% CI: 0.80-2.37) SMR=1.34 (95% CI: 0.61-2.54) SMR=1.39 (95% CI: 0.38-3.56) SMR=2.15 (95% CI: 0.05-11.94) SMR=0.60 (95% CI: 0.12-1.75) SMR=0.92 (95% CI: 0.34-2.00)	Mortality from pharyngeal, laryngeal and trachea/bronchus/lung cancer was not increased. Mortality from rectal, colon, oesophagus or breast cancer was not increased. Increased (but not significantly) mortality for cancer of buccal cavity and for other respiratory system cancer, a category that includes nasal cancers, because of 2 pleural cancers. No cases of nasopharyngeal (0.96 expected) and nasal (0.16 expected) cancers. Non-significant excess in myeloid leukaemia mortality. ML mortality increased with duration of exposure and time since first exposure although trend is not significant. Myeloid leukaemia mortality significantly increased in workers with first exposure more that 20 years ago.	Pinkerton 2004 (follow-up of Stayner 1985 and 1988)

Wood dust cohort 2 large furniture factories in Estonia using formaldehyde-based glue from 1960 n=6416 workers employed between 1946 and 1988 and exposed to a medium or high level of wood dust. Reference: estonian population mortality	Subjects were regarded as possibly exposed to FA if they had worked at least for 6 months since 1960 in the departments using glue The proportion of workers exposed to FA in the cohort is not given.	All cancer sites Buccal cavity Pharynx Colon Rectum Nose and sinuses Larynx Bronchi and lung Brain Haematopoietic and lymphatic: Non Hodgkin's lymphoma: Hodgkin's disease Leukaemia	No expo: SIR=1.16 (0.98-1.37) Possible expo: SIR=0.99 (0.90-1.09) No expo: SIR=1.58 (0.43-4.05) Possible expo: SIR=1.25 (0.62-2.23) No expo: SIR=3.57 (0.97-9.14) Possible expo: SIR=1.17 (0.38-2.73) No expo: SIR=1.69 (0.81-3.12) Possible expo: SIR=1.68 (1.19-2.30) No expo: SIR=0.79 (0.22-2.02) Possible expo: SIR=1.52 (1.01-2.19) No expo: SIR=2.94 (0.09-16.38) Possible expo: SIR=1.71 (0.21-6.17) No expo: SIR=0.42 (0.01-2.35) Possible expo: SIR=0.75 (0.27-1.62) No expo: SIR=1.24 (0.81-1.82) Possible expo: SIR=0.97 (0.76-1.23) No expo: SIR=1.88 (0.39-5.48) Possible expo: SIR=1.27 (0.58-2.40) No expo: SIR=1.45 (0.66-2.75) Possible expo: SIR=0.61 (0.34-1.00) No expo: SIR=1.32 (0.16-4.75) Possible expo: SIR=0.33 (0.04-1.20) No expo: SIR=2.99 (0.36-10.78) Possible expo: SIR=0.98 (0.20-2.87) No expo: SIR=1.51 (0.49-3.52) Possible expo: SIR=0.79 (0.38-1.45)	Stomach, rectum, larynx and kidney cancer risks were higher in workers possibly exposed to FA but only increase of rectum cancer risk reaches statistical significance. No case of nasopharyngeal cancer. Significantly elevated risk of colon cancer was also observed in workers possibly exposed to FA but similarly to what is seen in FA unexposed workers.	Innos 2000

MMVF cohort 10 US fibreglass production plants n=32000 workers employed for at least 1 year between 1945 and 1978 Follow-up through 1992 Reference: US and local death rates	22% of person-years exposed to FA with a median exposure of 0.066 ppm (range: 0.03-0.09 ppm)	Overall cancer Buccal cavity/pharynx Respiratory Larynx Bronchus/trachea/lung All lymphatic and hematopoietic tissues	SMR=0.98 (95% CI: 0.94-1.02) SMR=1.07 (95% CI: 0.82-1.37) **SMR=1.16 (95% CI: 1.08-1.24)** SMR=1.04 (95% CI: 0.70-1.50) **SMR=1.17 (95% CI: 1.09-1.25)** SMR=0.92 (95% CI: 0.80-1.06) RR for respiratory system cancers in FA-exposed workers adjusted for smoking : **RR=1.61 (95% CI: 1.02-2.57)**	See also the nested case-control study by Youk 2001 described hereafter. Excess of respirator cancers largely due to excess of bronchus/trachea/lung cancers. No specific information on nasal and sinonasal cancers.	Marsh 2001
One US fibreglass manufacturing plant n=4631 workers employed in the plant Reference: national or local mortality rates		All cancers Lung Buccal cavity/pharynx Brain Lymphohaematopoietic Leukaemia	SMR=0.96 (95% CI: 0.77-1.15) SMR=1.26 (95% CI: 0.93-1.68) SMR=0.70 (95% CI: 0.08-2.52) SMR=1.48 (95% CI: 0.54-3.23) SMR=0.46 (95% CI: 0.15-1.08) SMR=0.24 (95% CI: 0.006-1.36)	Nasopharynx and nasal cavity not reported.	Chiazze 1997
Woodworker cohort n=363 823 men occupationally exposed to wood dust between 1982 and 1988 (included in the American Cancer Society Cancer Prevention Study II)	387 woodworkers exposed to FA	All cancers Lung cancer Stomach cancer Lymphohaematopoietic Leukaemia	FOR: SMR=0.98 (95% CI:0.86-1.12) FOR+wood: SMR=1.61 (95% CI: 0.95-2.72) FOR: SMR=0.93 (95% CI: 0.73-1.18) FOR+wood: SMR=2.63 (95% CI: 1.25-5.51) FOR: SMR=1.63 (95% CI: 0.94-2.86) FOR+wood: SMR=0 FOR: SMR=1.22 (95% CI: 0.84-1.77) FOR+wood: SMR=3.44 (95% CI: 1.11-10.68) FOR: SMR=0.96 (95% CI: 0.54-1.71) FOR+wood: SMR=5.79 (95% CI: 1.44-23.25)	Increase in risk of lung cancers and of lymphatic and haematopoietic cancers due to leukaemia in woodworkers exposed to FA. In subjects exposed to FA only, stomach cancer risk was non-significantly increased. No nasal or nasopharynx cancers reported.	Stellman 1998

Danish industrial cohort 256 Danish companies in which formaldehyde was used. 2041 men and 1263 women with cancer were identified (standardised proportionate incidence) Reference: age-, sex and period-incidence of cancer among all Danish employees	Exposure assessed by job history (provided by Supplementary Pension Fund registries) with white-collar assumed to have low exposure and blue-collar high exposure.	Lung Nasal cavity Buccal cavity/pharynx Nasopharynx Larynx Brain Leukaemia	SPICR=1.0 (95% CI: 0.9-1.1) **SPICR=2.3 (95% CI: 1.3-4.0)** SPICR=1.1 (95% CI: 0.7-1.7) SPICR=1.3 (95% CI: 0.3-3.2) SPICR=0.9 (95% CI: 0.6-1.2) SPICR=1.1 (95% CI: 0.9-1.5) SPICR=0.8 (95% CI: 0.6-1.6)	Excess of nasal cancer was more pronounced among blue-collar exposed to FA only and with co-exposure to wood dust. SPIR was 3.0 (95% CI: 1.4-5.7) in men exposed to FA with no wood dust exposure and 5.0 (95% CI: 0.5-13.4) in men with FA and wood dust exposure. Two of the 13 "exposed" sino-nasal cancer cases provided no evidence in their job history for FA exposure. Three cases were adenocarcinomas, 6 squamous cell carcinomas and others unknown or other histological type. For leukaemia, lung and brain cancers no trend with increasing exposure.	Hansen 1995
Iron foundry n=3929 employed for 6 months or longer exposed to formaldehyde from 1960 to mid-1987 Follow-up through 1989 Reference: US national mortality rates	Assessment of exposure to FA based on a job-exposure matrix	All cancers Lung Buccal cavity/pharynx Larynx Brain All lymphohaematopoietic Leukaemia	SMR=0.99 (95% CI: 0.82-1.17) SMR=1.20 (95% CI: 0.89-1.58) SMR=1.31 (95% CI: 0.48-2.86) SMR=0.98 (95% CI: 0.11-3.53) SMR=0.62 (95% CI: 0.07-2.23) SMR=0.59 (95% CI: 0.23-1.21) SMR=0.43 (95% CI: 0.05-1.57)	Risk was similar for lung cancer and higher for buccal/pharyngeal cancer in unexposed workers.	Andjelkovich 1994, 1995

Italian formaldehyde resin plant n=1332 male workers employed for at least 30 days between 1959 and 1980 Follow-up through 1986 Reference: age and calendar-adjusted national and local mortality rates	Work history obtained from interview. Mean exposure measurement between 1974 and 1979: 0.17-3.15 ppm	Lung Lymphohaematapoietic	SMR=1.56 (95% CI: 1.0-2.32) SMR=1.80 (95% CI: 0.72-3.7)	Deficit in lung cancer in workers definitely exposed to FA (6 cases vs 8.7 expected) SMR were decreased with local rates comparisons No death from cancer in the nasal cavity. Data not reported for NPC, buccal cavity/pharynx, brain or leukaemia specifically.	Bertazzi 1989
Plastic manufacturing and R&D facility (USA) n=5932 male workers employed at a for at least 7 months between 1946 and 1967. Follow-up through 1988 Reference: national and local mortality rates	Only 111 of the cohort member were exposed to FA	Lung Other resp. system Pancreas	SMR=1.10 (95% CI: 0.92-1.31) SMR=3.73 (95% CI: 1.21-8.70) SMR=1.46 (95% CI: 0.95-2.16)	No cases of nasal or nasopharyngeal cancer. Excess of other respiratory system cancers due to an excess of pleural mesothelioma most likely attributable to exposure to asbestos.	Dell 1995

Swedish abrasive industry using formaldehyde resins n=911 workers employed for at least 5 years between 1955 and 1983 Follow-up through 1983 for mortality and 1981 for morbidity	Levels of FA: 0.08-0.81 ppm during manufacture of grinding wheels bound by FA resins. 59 workers had manufactured abrasive belt, with low exposure to abrasaives but intermittent, heavy exposure to FA with peaks up to 16-24 ppm.	All cancers Lung Stomach Colon Pancreas Prostate Lymphoma (non-Hodgkin) Multiple myeloma	Blue collar workers (521) SMR=0.93 (95% CI: 0.5-1.5) SIR=0.84 (95% CI: 0.54-1.25) SIR=0.57 (95% CI: 0.07-2.06) SIR=0.80 (95% CI: 0.1-2.9) SIR=1.0 (95% CI: 0.1-2.9) SIR=1.8 (95% CI: 0.2-6.6) SIR=0.85 (95% CI: 0.2-2.2) SIR=2.0 (95% CI: 0.2-7.2) SIR=4.0 (95% CI: 0.5-14.4)	No cases of leukaemia, nasal or buccal cancer. One case of nasopharyngeal cancer was observed (risk estimate not specified) and had a low exposure to FA (<0.08 ppm) and a relatively short exposure to FA (5 years). One of brain/CNS cancer was also reported (risk estimate not specified) (IARC 2006).	Edling 1987

Finnish women cohort N=413 877 women born between 1906 and 1945 who reported an occupation in the national census in 1970 excluding the two highest social classes and farmers. Follow-up from 1971 to 1995 Reference: national stratum-specific rates of economically active women.	Exposure assessed through job title from 1960 to 1984 and national job-exposure matrix. Job title were grouped into 3 exposure categories: unexposed, low intensity (less than 0.3 ppm), medium/high intensity (more than 0.3 ppm).	Brain and nervous system cancer	Low exposure: SIR=1.05 (95% CI: 0.93-1.19) Medium/high exposure: SIR=1.01 (95% CI: 0.77-1.32)	No adjustement for general lifestyle. The number of subject exposed to FA in the cohort is not known.	Wesseling 2002

4.10.2.2 Professional cohort studies

Table 20: Professional cohort studies

Cohort description	Estimation of exposure	Cancer site	Risk estimate	Observations and remarks	Ref

British pathologist cohort Royal College of Pathologists and the Pathological society. n=4512 alive members in 1955 Follow-up through 1986 Reference: sex-specific England and Wales (E/W) or Scotland mortality rates	No assessment of FA exposure	All cancers Lung Brain Lymphohaematopoietic Leukaemia Breast Prostate	Men (E/W) : SMR=0.4 (95% CI: 0.3-0.6) Men (Scotl.): SMR=0.6 (95% CI: 0.3-1.1) Women (E/W) : SMR=1.0 (95% CI: 0.5-1.9) Combined: SMR=0.5 (95% CI: 0.4-0.6) Combined: SMR=0.2 (95% CI: 0.1-0.4) Men (E/W) : SMR=2.4 (95% CI: 0.9-5.2) Combined: SMR=2.2 (95% CI: 0.8-4.8) Men (E/W) : SMR=1.4 (95% CI: 0.7-2.7) Combined: SMR=1.5 (95% CI: 0.4-3.9) Women (E/W) : SMR=1.6 (95% CI: 0.4-4.1) Men (Scotl.): SMR=3.3 (95% CI: 0.4-12)	No excess observed at any other cancer site. No nasal or nasopharyngeal cancers reported. In a previous study, non-significant excess of lymphohaematopoietic cancers was observed among pathologists but not among technicians with no excess in leukaemia in either group.	Hall 1991
US embalmer cohort (NY) n=1132 white men licensed as embalmers between 1902 and 1980 in New-York state and who died between 1925 and 1980 Reference: age-, sex-, race- and calendar time-specific national mortality rates	No assessment of formaldehyde exposure	All cancers Buccal/pharynx Lung Brain Lymphohaematopoietic Lymphoma Leukaemia Myeloid leukaemia	PMR=1.1 (95% CI: 1.0-1.3) PMR=1.0 (95% CI: 0.4-2.0) PMR=1.1 (95% CI: 0.9-1.4) PMR=1.4 (95% CI: 0.6-2.7) PMR=1.2 (95% CI: 0.8-1.8) PMR=0.8 (95% CI: 0.3-1.9) PMR=1.2 (95% CI: 0.6-2.1) PMR=1.5 (95% CI: 0.5-3.19)	No death from cancer of nasal sinuses or nasopharynx (0.5 expected). Risks of brain and buccal/pharynx cancer mortality were increased in embalmers only (not significant) but not in funeral directors. Risk of lymphohaematopoietic cancer mortality was increased in funeral directors (not significant) but not in embalmers only. Embalmers are assumed to have had more exposure than funeral directors.	Walrath 1983

US embalmer cohort (CA) n=1007 white men licensed as embalmers between 1916 and 1978 in Califormia and who died between 1925 and 1980 Reference: age-, sex-, race- and calendar time-specific national mortality rates	No assessment of formaldehyde exposure	All cancers Buccal/pharynx Lung Brain Lymphohaematopoietic Lymphoma Leukaemia Myeloid leukaemia Prostate Colon	PMR=1.2 (95% CI: 1.0-1.4) PMR=1.3 (95% CI: 0.6-2.6) PMR=0.9 (95% CI: 0.6-1.2) PMR=1.9 (95% CI: 0.9-3.6) PMR=1.2 (95% CI: 0.7-1.9) PMR=1.0 (95% CI: 0.2-2.8) PMR=1.8 (95% CI: 0.9-3.0) PMR=1.5 (95% CI: 0.6-3.3) PMR=1.8 (95% CI: 1.1-2.6) PMR=1.9 (95% CI: 1.3-2.7)	No death from cancer of nasal sinuses or nasopharynx (0.6 expected). A trend with duration was observed for leukaemia (PMR=2.2 (95% CI: 1.0-4.4) among embalmers licensed for 20 years or more) and for prostate cancer. No trend for duration of exposure for buccal/pharynx cancers.	Walrath 1984
Canadian embalmer cohort n=1413 males licensed as embalmers between 1928 and 1957 in Ontario and who died between 1950 and 1977 Reference: age- and calendar time-specific Ontario mortality rates	No assessment of formaldehyde exposure	All cancers Buccal/pharynx Lung Brain Lymphohaematopoietic Leukaemia	SMR=0.9 (95% CI: 0.7-1.1) SMR=0.5 (95% CI: 0.01-2.7) SMR=0.9 (95% CI: 0.6-1.5) SMR=1.2 (95% CI: 0.2-3.4) SMR=1.2 (95% CI: 0.5-2.4) SMR=1.6 (95% CI: 0.4-4.1)	No death from cancer of nose, middle ear or nasal sinuses (0.2 expected).	Levine 1984
American anatomist cohort n=2239 males members of the American Association of Anatomists between 1888 and 1969 and who died between 1925 and 1979 Reference: age-, race-, sex- and calendar time-specific national mortality rates or mortality in the American Psychiatric Association	No assessment of formaldehyde exposure	All cancers Buccal/pharynx Lung Brain Lymphohaematopoietic Lymphoma Leukaemia Myeloid leukaemia	SMR=0.6 (95% CI: 0.5-0.8) SMR=0.2 (95% CI: 0.0-0.8) SMR=0.9 (95% CI: 0.6-1.5) SMR=2.7 (95% CI: 1.3-5.0) SMR=1.2 (95% CI: 0.7-2.0) SMR=0.7 (95% CI: 0.1-2.5) SMR=1.5 (95% CI: 0.7-2.7) SMR=8.8 (95% CI: 1.8-25.5)	No death from nasal cancer (0.5 expected). A trend with duration was observed for brain cancer but not for leukaemia. Deficit of lung cancer and leukaemia when compared with mortality rates in the American Psychiatric Association but excess of brain cancer (SMR=6.0 (95% CI: 2.3-16).	Stroup 1986

American embalmer cohort n=4046 deceased males licensed as embalmers/funeral directors between 1975 and 1985 Reference: 5-year age-, race-, sex- and calendar time-specific national mortality rates	No assessment of formaldehyde exposure	All cancers Buccal/pharynx Nasopharynx Lung Brain Lymphohaematopoietic Lymphoma Lymphatic leukaemia Myeloid leukaemia Other/unspecified leukaemia	White men : SMR=1.1 (95% CI: 1.0-1.2) Non-white men: SMR=1.1 (95% CI: 0.9-1.3) White men : SMR=1.2 (95% CI: 0.8-1.7) Non-white men: SMR=1.3 (95% CI: 0.3-3.2) White men : SMR=1.9 (95% CI: 0.4-5.5) Non-white men: SMR=4.0 (95% CI: 0.1-22) White men : SMR=1.0 (95% CI: 0.9-1.1) Non-white men: SMR=0.8 (95% CI: 0.5-1.1) White men : SMR=1.2 (95% CI: 0.8-1.8) White men : SMR=1.3 (95% CI: 1.1-1.6) Non-white men: SMR=2.4 (95% CI: 1.4-4.0) White men : SMR=1.1 (95% CI: 0.5-1.9) Non-white men: SMR=1.9 (95% CI: 0.1-11) White men : SMR=0.6 (95% CI: 0.2-1.3) Non-white men: SMR=3.0 (95% CI: 0.4-11) White men : SMR=1.6 (95% CI: 1.0-2.4) Non-white men: SMR=1.1 (95% CI: 0.1-5.9) White men : SMR=2.1 (95% CI: 1.2-3.3) Non-white men: SMR=4.9 (95% CI: 1.0-14.4)	No death from nasal cancer (1.8 expected).	Hayes 1990

4.10.2.3 Case-control studies

The studies are listed by cancer site.

Table 21: Case-control studies

Cancer site	Study population	Estimation of exposure	Results	Observations and remarks	Ref

Sinonasal cancer (nasal cavity and sinuses)	Cases: 160 patients from 2 US states diagnosed between 1970 and 1980 Controls: 290 country-, age- and sex-matched controls with other conditions	Occupational exposure assessed through direct or proxy-interview in two categories: ever/never.	OR: 0.35 (95% CI: 0.1-1.8)	Only two cases employed in industry were reported with exposure to FA.	Brinton 1984
Sinonasal cancer (sinonasal cavities)	Cases: 525 patients from Denmark diagnosed between 1970 and 1982 Controls: 2465 controls matched for age, sex and year of diagnosis with colon, rectum, prostate or breast cancers	Occupational history collected from the national pension registries and exposure assessed by industrial hygienists	Men with definite exposure to FA: **OR: 2.8 (95% CI: 1.8-4.3)** - Unexposed to wood dust: OR: 1.8 (95% CI: 0.7-4.9) - Exposed to wood dust: **OR: 3.5 (95% CI: 2.2-5.6)** Men with probable exposure to FA: OR: 1.2 (95% CI: 0.8-1.7)	Adjustment for wood exposure decreased risk estimate of men with definite exposure to 1.6 (95% CI: 0.7-3.6).	Olsen 1984
Sinonasal cancer (nasal cavities and paranasal sinuses)	Cases: 215 men with squamous cell carcinoma and 39 with adenocarcinoma from Denmark diagnosed between 1970 and 1982 Controls: 2465 controls matched for age, sex and year of diagnosis with colon, rectum, prostate or breast cancers	Occupational history collected from the national pension registries and exposure assessed by industrial hygienists	<u>Squamous cell carcinoma :</u> OR: 2.3 (95% CI: 0.9-5.8), based on 13 exposed cases (8 for more than 10 years) of which 4 (2 for more than 10 years) were unexposed to wood dust. Exposure > 10 years: OR: 2.4 (95% CI: 0.8-7.4) <u>Adenocarcinoma :</u> OR: 2.2 (95% CI: 0.7-7.2), based on 17 exposed cases (12 for more than 10 years) of which 1 (1 for more than 10 years) was unexposed to wood dust. Exposure > 10 years: OR: 1.8 (95% CI: 0.5-6.0)	OR adjusted for wood dust exposure.	Olsen 1986 (reanalys is of Olsen 1984)

Sinonasal cancer (epithelial cancer of the nasal cavity or paranasal sinuses)	Cases: 91 men from the Netherlands diagnosed between 1978 and 1981 Controls: 195 controls matched for age and sex	Occupational history collected from personal interviews and exposure assessed by two independent industrial hygienists and classified according to level and probability from 0 to 9.	**Hygienist A: OR: 2.5 (95% CI: 1.5-4.3)** **Hygienist B: OR: 1.9 (95% CI: 1.2-3.0)** In subjects with moderate/high exposure to wood dust: Hygienist A: OR: 1.9 (95% CI: 0.7-5.5) Hygienist B: not determined In subjects with little/no exposure to wood dust and adjustment for tobacco use: **Hygienist A: OR: 2.2 (95% CI: 1.1-4.6.0)** Hygienist B: OR: 1.6 (95% CI: 0.9-2.8) RR increases with level of exposure to FA with both hygienists. Squamous cell carcinoma in subjects with little/no exposure to wood dust: **Hygienist A: OR: 3.0 (95% CI: 1.3-6.4)** Hygienist B: OR: 1.9 (95% CI: 1.0-3.6) RR increases with level of exposure to FA with both hygienists. No such relationship found for adenocarcinomas which could only be examined in the moderate/high wood dust exposure group.	Analyses controlled for history of tobacco use, which was not shown to be a confounder. A large excess of risk of adenocarcinomas was associated with high exposure to wood dust.	Hayes 1986

Sinonasal cancer	Cases: 53 sinonasal cancer cases diagnosed between 1979 and 1983 Controls: 552 age and-sex-matched controls identified by random-digit dialing	Occupational history collected from telephone interviews and exposure assessed by a job-exposure linkage system (probability and level of exposure) and by the duration of exposure. Exposure score: exposure level weighted by duration of exposure	Level of exposure (values not specified): Low exposure: OR: 0.8 (95% CI: 0.4-1.7) Medium/high exposure : OR: 0.3 (95% CI: 0.0-1.3) Duration of exposure: 1-9 years of exposure: OR: 0.7 (95% CI: 0.3-1.4) ≥ 10 years of exposure: OR: 0.4 (95% CI: 0.1-1.9) Exposure score: 5-19 exposure score: OR: 0.5 (95% CI: 0.1-1.6) ≥ 20 exposure score: OR: 0.3 (95% CI: 0.0-2.3)	OR adjusted for sex, age, cigarette smoking and alcohol intake. Living in a mobile home was not associated with an increase of sinonasal cancer risk whereas living in residences constructed with particle-boards was associated with a not-significantly increased risk.	Vaughan 1986a
Sinonasal cancer	Cases: 198 sinonasal cancer cases (male) from Connecticut who died between 1935 and 1975 Controls: 552 men who died in Connecticut in the same period	Occupational history collected from death certificates and annual city directories. Occupations were assessed by an industrial hygienist (probability and level of exposure).	Probably exposed for most of working life: OR: 0.8 (95% CI: 0.5-1.3) Probably exposed for most of working life + exposed 20 or more years before death: OR: 1.0 (95% CI: 0.5-1.8) Probably exposed for most of working life + to high level for some years: OR: 1.0 (95% CI: 0.5-2.2) Probably exposed for most of working life + to high level at some point 20 or more years before death: OR: 1.5 (95% CI: 0.6-3.9)	OR adjusted for age at death, year of death and number of jobs reported.	Roush 1987

Sinonasal cancer (nasal cavities and parasinuses)	Cases: 207 patients from French hospitals diagnosed between 1986 and 1988 Controls: 409 age- and sex-matched controls (healthy individuals or patients with another cancer)	Occupational history collected from personal interview and exposure assessed by an industrial hygienist.	Squamous cell nasal carcinoma in men with probable/definite exposure (n=59): Low cumulative exposure: OR: 1.26 (95% CI: 0.54-2.94) High cumulative exposure: OR: 0.68 (95% CI: 0.27-1.71) Adenocarcinoma in men with probable/definite exposure (n=67): Low cumulative exposure: OR: 1.13 (95% CI: 0.19-6.90) Medium cumulative exposure: OR: 2.66 (95% CI: 0.38-18.7) **High cumulative exposure: OR: 6.91 (95% CI: 1.69-28.3)**	OR adjusted for age and exposure to wood and glue. For adenocarcinoma, only 4 cases were not exposed to wood dust and OR for exposure to FA only was 8.1 (95% CI: 0.9-73).	Luce 1993
Sinonasal cancer (nasal cavities and parasinuses)	Cases: 86 male workers in the German wood industry with adenocarcinomas and with a recognised occupational disease between 1994 and 2003 Controls: 204 age-matched workers in the German wood industry with a recognised ccupational disease (fall accident or accident on the way) between 1994 and 2003	Occupational history, lifestyle factor and medical data collected from a structured questionnaire to the subject or next of kin and exposure to formaldehyde semi-quantitatively assessed by an expert team.	Exposure to formaldehyde: < 1985: OR: 0.46 (95% CI: 0.14-1.54) based on 8 cases and 17 controls ≥ 1985: OR: 0.94 (95% CI: 0.47-1.90) based on 39 cases and 95 controls	OR adjusted for smoking, age, region, interviewee and average exposure to wood dust.	Pesch 2008

Sinonasal cancer	**Pooled analysis** of 12 case-control studies from 7 countries Cases: 195 adenocarcinoma and 432 squamous cell carcinoma of the nasal cavity and paranasal sinuses (total: 930) Controls: 3136 subjects	Occupational history collected by various methods. Exposures assessed through a job-exposure matrix (probability and intensity). Levels of exposure defined as a 8-h TWA concentrations: Low exposure: <0.25 ppm Medium exposure: 0.25-1 ppm High exposure: > 1 ppm	OR adjusted for age and study, and for cumulative exposure to wood dust and leather dust for adenocarcinomas in men. Men: Squamous cell carcinoma: Low exposure: OR: 1.2 (95% CI: 0.8-1.8) Medium exposure: OR: 1.1 (95% CI: 0.8-1.6) High exposure: OR: 1.2 (95% CI: 0.8-1.8) Adenocarcinoma: Low exposure: OR: 0.7 (95% CI: 0.3-1.9) Medium exposure: OR: 2.4 (95% CI: 1.3-4.5) **High exposure: OR: 3.0 (95% CI: 1.5-5.7)** Women: Squamous cell carcinoma: Low exposure: OR: 0.6 (95% CI: 0.2-1.4) Medium exposure: OR: 1.3 (95% CI: 0.6-3.2) High exposure: OR: 1.5 (95% CI: 0.6-3.8) Adenocarcinoma: Low exposure: OR: 0.9 (95% CI: 0.2-4.1) Medium exposure: no case **High exposure: OR: 6.2 (95% CI: 2.0-19.7)**	Significant increase in adenocarcinoma risk in both sexes. Non-significant slight increase in squamous cell carcinoma. All exposure variables (probability, maximum level and duration) were associated with adenocarcinomas. In subjects never exposed to wood dust and with high cumulative exposure to FA adenocarcinoma risk was 1.9 (95%: 0.5-6.7) in men and 11.1 (95%: 3.2-38.0) in women.	Luce 2002

Oral cavity or oropharynx cancer	Cases: 86 men from Turin diagnosed with oral cavity cancer (n=74) or oropharynx cancer (n=12) between 1982-84. Controls: 373 male residents of Turin matched for age	Occupational history collected from personal interview. Frequency and intensity of exposure assessed from a job-exposure matrix developed by IARC and subjects were grouped into three categories of presumed frequency and intensity.	Any exposure to FA: OR=1.6 (95% CI: 0.9-2.8) (25 exposed cases) Probable or definite exposure: OR=1.8 (95% CI: 0.6-5.5) (only 6 exposed cases) No trend with duration of exposure.	OR after adjustment for age, smoking, alcohol consumption and other potential confounder.	Merletti 1991
Oral cancer (squamous cell carcinoma)	Cases: 128 men with cancer of the oral cavity diagnosed between 1988 and 1991 in two Swedish regions Controls: 641 men matched for age and location	Occupational history collected from interview and structured questionnaire. Exposure assessed by an industrial hygienist (probability and intensity).	RR=1.28 (95% CI: 0.64-2.54) based on 14 exposed cases.	RR adjusted for region, age, alcohol intake and tabacco smoking.	Gustavs-son 1998

Salivary gland cancer	Cases: 2405 subjects who died from salivary gland cancer between 1984 and 1989 in 24 US states Controls: 9420 age-, race-, gender- and state-matched subjects who died from non-infectious causes	Usual occupation was obtained by death certificate. Probability and intensity of exposure to formaldehyde and numerous solvents was assessed by a job-exposure matrix	White men (1347 cases/5388 controls) Low probability/low intensity: OR: 0.9 (95% CI: 0.70-1.15) Low probability/mid-high intensity: OR: 0.7 (95% CI: 0.35-1.26) Mid-high probability/low intensity: OR: 2.4 (95% CI: 0.86-6.75) Mid-high probability/mid-high intensity: **OR: 1.6 (95% CI: 1.30-2.00)** **Trend: p<0.001** White women (890 cases/3360 controls) Low probability/low intensity: OR: 0.7 (95% CI: 0.33-1.28) Low probability/mid-high intensity: OR: 1.1 (95% CI: 0.54-2.07) Mid-high probability/low intensity: OR: 1.3 (95% CI: 0.63-2.60) Mid-high probability/mid-high intensity: OR: 1.0 (95% CI: 0.73-1.49) Trend: p=0.69 African American women (75 cases/300 controls) Mid-high probability/mid-high intensity: OR: 1.9 (95% CI: 0.75-5.06) No increase for African American men or other categories of African American women.	OR adjusted for age, marital status and socio-economic status. Significant trend and increase in mortality in mid-high probability and intensity white men but no dose response pattern. Certain occupations with known FA exposure were at increased risk: white men employed as physicians: OR: 3.6 (95% CI: 1.75-7.24) White men employed in furniture sales: OR: 3.7 (95% CI: 1.06-12.83) White women employed as dressmakers: OR: 2.6 (95% CI: 0.93-7.20)	Wilson 2004

Nasopharyngeal cancer	Cases: 23 cases of pharyngeal cancer in the cohort of Marsh 2007a (plant 1 of NCI cohort) including 7 NPC. Controls: 92 controls matched for age, sex, race and year of birth from the same cohort.	Median average intensity of exposure: 0.138 ppm in the 5649 exposed workers. Information on employment history obtained from survey data, pre-employment application forms at Wallingford and city directories and aided by a genealogist.	<u>OR for NPC adjusted for age, race, sex and year of birth:</u> Smoking status: Never: OR: 1.00 Ever: OR: 3.04 (95% CI: 0.33-∞) Unknown: OR: 0.38 (95% CI: 0.03-∞) Silver smithing: Never: OR: 1.00 **Ever: OR: 14.41 (95% CI: 1.30-757.8)** Unknown: OR: 3.31 (95% CI: 0-42.4) Other metal work: Never: OR: 1.00 Ever: OR: 3.61 (95% CI: 0.50-22.7) Unknown: OR: 5.04 (95% CI: 0-68.0) Silver smithing or other metal work: Never: OR: 1.00 **Ever: OR: 7.31 (95% CI: 1.08-82.1)** Unknown: OR: 7.15 (95% CI: 0-104.4) Formaldehyde: Unexposed: OR: 1.00 Exposed: OR: 1.51 (95% CI: 0.20-∞) <u>OR for NPC further adjusted for smoking and working in silver smithing or other metal work:</u> Formaldehyde: Unexposed: OR: 1.00 Exposed: OR: 2.87 (95% CI: 0.21-∞)	4 of the 7 NPC cases had a non-Wallingford employment in silver-smithing and 1 in other metal work. 4 of the 16 cases of all other pharyngeal cancers had employment in other metal work, yielding a not statistically significant 1.40 increase in OR.	Marsh 2007a

			Duration of exposure: < 1 y: OR: 1.00 1-9 y: OR: 1.81 (95% CI: 0.03-36.4) ≥ 10 y: OR: 2.72 (95% CI: 0.16-145.6) Cumulative exposure (ppm-year): < 0.004: OR: 1.00 0.004-0.219: OR: 1.65 (95% CI: 0.03-173.1) ≥ 0.22: OR: 5.91 (95% CI: 0.16-950.3) Average intensity of exposure (ppm): < 0.03: OR: 1.00 0.03-0.159: OR: 11.41 (95% CI: 0.80-668.5) ≥ 0.16: OR: 2.18 (95% CI: 0.09-133.8)	Increasing trend in OR with increasing duration and cumulative exposure to FA but none of OR nor trends statistically significant. Categorisation with peak not analysed.	
Nasopharyngeal cancer	Cases: 215 men and 99 women from Denmark diagnosed between 1970 and 1982 Controls: 2465 controls matched for age, sex and year of diagnosis with colon, rectum, prostate or breast cancers	Occupational history collected from the national pension registries and exposure assessed by industrial hygienists	Men: OR: 0.7 (95% CI: 0.3-1.7) Women: OR: 2.7 (95% CI: 0.3-21.9)		Olsen 1984

Nasopharyngeal cancer	Cases: 27 nasopharyngeal cases diagnosed between 1980 and 1983 Controls: 552 age and sex-matched controls identified by random-digit dialing	Occupational history collected from telephone interviews and exposure assessed by a job-exposure linkage system (probability and level of exposure) and by the duration of exposure. Exposure score: exposure level weighted by duration of exposure	Low exposure: OR: 1.2 (95% CI: 0.5-3.3) Medium/high exposure : OR: 1.4 (95% CI: 0.4-.7) Highest exposure score: OR: 2.1 (95% CI: 0.4-10.0) 1-9 years of exposure: OR: 1.2 (95% CI: 0.5-3.1) ≥ 10 years of exposure: OR: 1.6 (95% CI: 0.4-5.8) 5-19 exposure score: OR: 0.9 (95% CI: 0.2-3.2) ≥ 20 exposure score: OR: 2.1 (95% CI: 0.6-7.8)	OR adjusted for sex, age, cigarette smoking and alcohol intake. Living in a mobile home for more than 10 years was associated with a significant increase of nasopharyngeal cancer risk **(OR: 5.5 (95% CI: 1.6-19)** based on 4 exposed cases.	Vaughan 1986a and b
Nasopharyngeal cancer	Cases: 173 nasopharyngeal cancer cases (male) from Connecticut who died between 1935 and 1975 Controls: 552 men who died in Connecticut in the same period	Occupational history collected from death certificates and annual city directories. Occupations were assessed by an industrial hygienist (probability and level of exposure).	Probably exposed for most of working life: OR: 1.0 (95% CI: 0.6-1.7) + exposed to high level for some years: OR: 1.4 (95% CI: 0.6-3.1) + exposed to high level at some point 20 or more years before death: OR: 2.3 (95% CI: 0.9-6.0)	OR adjusted for age at death, year of death and number of jobs reported.	Roush 1987

Nasopharyngeal cancer	Cases: 104 cases of nasopharyngeal carcinoma from the Philippines General Hospital Controls: 193 controls matched for age, sex and location.	Occupational history collected from personal interview and exposure assessed by an industrial hygienist.	**< 15 years: OR: 2.7 (95% CI: 1.1-6.6)** ≥ 15 years: OR: 1.2 (95% CI: 0.5-3.2) < 15 years (10-year lag): OR: 1.6 (95% CI: 0.6-3.8) ≥ 15 years (10-year lag): OR: 2.1 (95% CI: 0.7-6.2) Age ≥ 25 years at first exposure: OR: 1.2 (95% CI: 0.5-3.3) **Age < 25 years at first exposure: OR: 2.7 (95% CI: 1.1-6.6)** First exposure < 25 years before diagnosis: OR: 1.3 (95% CI: 0.6-3.2) **First exposure ≥ 25 years before diagnosis: OR: 2.9 (95% CI: 1.1-7.6)**	OR adjusted for other occupational exposure.	West 1993

Nasopharyngeal cancer (squamous cell carcinomas)	Cases: 282 Chinese cases with histologically confirmed NPC who had resided in Kuala Lumpur (Malaysia) for at least 5 years and diagnosed between 1987 and 1992 Controls: 282 controls matched for age and sex healthy subjects from the general Chinese population of Kuala Lumpur	Occupational and residential history, information on use of alcohol, tobacco, 55 food items collected from structured interview. Level of exposure assessed with reference to kind of job, job performed, mode of contact, respondent's reporting of exposure, years of exposure, frequency and duration and classified as ever/never, low, medium or high with reference to the work performed, duration and frequency.	Exposure to formaldehyde reported in 9.9% of cases and 8.2% of controls (p=0.25 when adjusted for diet and cigarette smoke) Unadjusted OR: 1.24 (95% CI: 0.67-2.32) Adjusted OR for smoke and diet: 0.71 (95% CI: 0.34-1.43) OR associated with a ten-fold ratio of hours exposed: Unadjusted: 1.04 (95% CI: 0.86-1.27) Adjusted: : 0.88 (95% CI: 0.70-1.12), p=0.29	Case and control groups differed in social class, Chinese subethnicity and education. Formaldehyde exposure was reported in only 51 of 564 subjects (9%) of the sample, of whom only eight had accumulated ≥10 years of exposure outside a 10-year latency period.	Armstrong 2000

Nasopharyngeal cancer (almost exclusively nonkeratinizing and undifferentiated carcinomas)	Cases: 375 cases with histologically confirmed nasopharyngeal carcinoma from Taipei. Controls: 325 age, sex- and district location-matched subjects	Job history collected from interviewed-administered questionnaire. Level of exposure classified by an industrial hygienist with reference to probability, intensity and duration of exposure to FA, wood and organic solvents.	19.7% of cases and 14.4 % of subjects were exposed to FA. RR: 1.4 (95% CI: 0.93-2.2) Increasing risk with increasing duration and cumulative exposure but trends not significant. 1-10 years: RR: 1.3 (95% CI: 0.69-2.3) 10-20 years: RR: 1.6 (95% CI: 0.91-2.9) > 20 years : RR: 1.7 (95% CI: 0.77-3.5)	In analyses restricted to cases (n=360) and controls (n=94) seropositive to Epstein-Barr virus antibodies: RR: 2.7 (95% CI: 1.2-6.2) Non-significant increase in risk with increasing years of exposure to FA in the absence of wood (trend: p=0.09)	Hildesheim 2001 (=Cheng 1999, = Hildesheim 1997)
Nasopharyngeal cancer (epithelial nasopharyngeal carcinoma)	Cases: 196 NPC cases from 5 US regional cancer registries Controls: 244 age- and sex-matched subjects selected by random digit dialing	Occupational history collected from interview. Exposure probability, mean exposure, frequency and duration assessed by an industrial hygienist.	40.3% of cases and 32.4 % of subjects were exposed to FA. OR: 1.3 (95% CI: 0.8-2.1) No significant trend with maximum exposure but increasing risk with increasing duration of work in potentially-exposed jobs. Association between FA exposure and NPC risk was stronger when analyses focused on jobs with higher probability of exposure: Possible/probable/definite exposure probability: **OR: 1.6 (95% CI: 1.0-2.8)** Significant trend with duration (p=0.014) and cumulative exposure (p=0.033) Probable/definite exposure probability: **OR: 2.1 (95% CI: 1.1-4.2)** Definite exposure probability: **OR: 13.3 (95% CI: 2.5-70)**	OR adjusted for age, sex, race, registration site, cigarette use, alcohol consumption and education. OR were essentially unaffected by wood dust exposure.	Vaughan 2000

Nasopharyngeal cancer	Cases: 4 deceased funeral directors and embalmers with NPC identified as cause of death. Controls: 265 individuals in the funeral industry with other cause of death and matched for age, sex and date of death. Cases and controls were part of the cohorts of Hayes 1990, Walrath 1983 or Walrath 1984.	Information on work practice and demographic characteristics were obtained by interview of one next to kin and several coworkers per subjects. Questionnaire responses were linked to a predictive model based on exposure-assessment data.	Four case subjects died from NPC but only two had embalmed. Average exposure levels of the two exposed case subjects were however equal to or higher than the corresponding levels among exposed control subjects for most exposure metrics. Due to the low number of cases it was however not possible to conclude.	OR adjusted for year of birth, age at death, sex, data source and smoking status.	Hauptmann 2009
Pharyngeal cancer	Cases: 22 cases of pharyngeal cancer in the cohort of Marsh 2002 (plant 1 of NCI cohort) Controls: 88 controls matched for age, sex, race and year of birth from the same cohort.	Median average intensity of exposure: 0.138 ppm in the 5665 exposed workers of the cohort.	Unexposed: OR: 1.00 Exposed: OR: 3.04 (95% CI: 0.36-145.58) Duration of exposure: < 1 y: OR: 1.00 1-9 y: OR: 1.01 (95% CI: 0.19-4.42) ≥ 10 y: OR: 2.23 (95% CI: 0.34-14.97) Cumulative exposure (ppm-year): < 0.004: OR: 1.00 0.004-0.219: OR: 0.89 (95% CI: 0.22-3.56) ≥ 0.22: OR: 0.81 (95% CI: 0.13-4.34)	OR adjusted for smoking and year of hire.	Marsh 2002

Oro- or hypopharyngeal cancer	Cases: 205 oro- or hypopharyngeal cases diagnosed between 1980 and 1983 Controls: 552 age and sex-matched controls identified by random-digit dialing	Occupational history collected from telephone interviews and exposure assessed by a job-exposure linkage system (probability and level of exposure) and by the duration of exposure. Exposure score: exposure level weighted by duration of exposure	Low exposure: OR: 0.8 (95% CI: 0.5-1.4) Medium exposure : OR: 0.8 (95% CI: 0.4-1.7) High exposure : OR: 0.6 (95% CI: 0.1-2.7) 1-9 years of exposure: OR: 0.6 (95% CI: 0.3-1.0) ≥ 10 years of exposure: OR: 1.3 (95% CI: 0.7-2.5) 5-19 exposure score: OR: 0.6 (95% CI: 0.3-1.2) ≥ 20 exposure score: OR: 1.5 (95% CI: 0.7-3.0)	OR adjusted for sex, age, cigarette smoking and alcohol intake. Living in a mobile home or living in residences constructed with particle-boards were not associated with an increase of oro- or hypopharyngeal cancer risk.	Vaughan 1986a
Oro- or hypopharyngeal cancer (squamous cell carcinoma)	Cases: 138 men with oro- or hypopharyngeal cancer diagnosed between 1988 and 1991 in two Swedish regions Controls: 641 men matched for age and location	Occupational history collected from interview and structured questionnaire. Exposure assessed by an industrial hygienist (probability and intensity).	RR=1.01 (95% CI: 0.49-2.07) based on 13 exposed cases.	RR adjusted for region, age, alcohol intake and tabacco smoking.	Gustavsson 1998

Hypopharyngeal cancer (squamous cell)	Cases: 201 men with hypopharyngeal squamous cell cancers from 15 French hospitals between 1989 and 1991. Controls: 296 age-and location-matched patients with primary cancers of different sites	Occupational history collected from interview. Exposure probability and level assessed through a job-exposure matrix.	OR: 1.35 (95% CI: 0.86-2.14) After excluding subjects with exposure probability < 10%: OR: 1.74 (95% CI: 0.91-3.34) Duration < 7 years : OR: 0.74 (95% CI: 0.20-2.68) Duration 7-20 years : OR: 1.65 (95% CI: 0.67-4.08) **Duration > 20 years : OR: 2.70 (95% CI: 1.08-6.73)** Cumulative low level: OR: 0.78 (95% CI: 0.11-5.54) Cumulative medium level: OR: 1.77 (95% CI: 0.65-4.78) Cumulative high level: OR: 1.92 (95% CI: 0.86-4.32) **In subjects with exposure probability > 50%: OR: 3.78 (95% CI: 1.50-9.49)**	OR adjusted for age, alcohol consumption, smoking, coal dust and asbestos. Dose-response pattern with the probability of exposure (p<0.005) and duration of exposure after exclusion of subjects with an exposure probability < 10% (p<0.04).	Laforest 2000
Hypolaryngeal cancer	Cases: 304 men with hypopharyngeal cancers from 6 centres in Southern Europe between 1979 and 1982. Controls: 2176 age- and centre-matched controls in general population	Occupational history collected from interview. Exposure probability assessed by a panel of occupational physicians, industrial hygienists and chemical engineers.	Possible exposure: OR: 1.3 (95% CI: 0.6-2.6) Probable or certain exposure: OR: 0.5 (95% CI: 0.1-1.8) No trend with duration of exposure.	OR adjusted for age, centre, alcohol, smoking, socio-economic status, diet and exposure to potential chemical confounders.	Berrino 2003

Hypopharyngeal and laryngeal cancer	Cases: 34 hypopharyngeal and 316 laryngeal male cancer cases diagnosed between 1999 and 2002 in four study centers in Central and Eastern Europe Controls: 728 male hospital controls matched for age	Occupational history collected from interview and structured questionnaire. Assessment of occupational exposure by local experts with practical experience in industrial hygiene.	Laryngeal cancer: OR=1.68 (95% CI: 0.85-3.31) based on 18 exposed cases and 30 exposed controls. OR increased with duration of exposure (p=0.06) and cumulative exposure (p=0.07). OR for the highest level of cumulative exposure (≥22,700 mg/m^3-hours): **3.12 (95% CI: 1.23-7.91)**. Hypopharyngeal cancer: OR not calculated as less than 10 exposed cases were identified.	OR adjusted for age, country, alcohol consumption and tabacco smoking.	Shangina 2006
Laryngeal cancer (squamous cell carcinoma)	Cases: 157 men with laryngeal cancer diagnosed between 1988 and 1991 in two Swedish regions Controls: 641 men matched for age and location	Occupational history collected from interview and structured questionnaire. Exposure assessed by an industrial hygienist (probability and intensity).	RR=1.45 (95% CI: 0.83-2.51) based on 23 exposed cases.	RR adjusted for region, age, alcohol intake and tabacco smoking.	Gustavs-son 1998

Laryngeal cancers	Cases: 296 men with histologically confirmed laryngeal squamous cell cancers from 15 French hospitals between 1989 and 1991. Controls: 296 age-and location-matched patients with primary cancers of different sites	Occupational history collected from interview. Exposure probability and level assessed through a job-exposure matrix.	OR: 1.14 (95% CI: 0.76-1.70) After excluding subjects with exposure probability < 10%: OR: 1.17 (95% CI: 0.63-2.17)	OR adjusted for age, alcohol consumption, smoking and coal dust. Slightly increased risk although not significant. No significant trend with probability, duration or cumulative level of exposure	Laforest 2000
Laryngeal cancer	Cases: 940 male subjects diagnosed with laryngeal cancer in a Turkish hospital between 1979 and 1984 Controls: 1519 male patients with neoplastic and non-neoplastic conditions	Occupational history collected from interview-administered questionnaire. Exposure probability and intensity assessed through a job-exposure matrix.	All locations: OR: 1.0 (95% CI: 0.8-1.3) Supraglottic tumours: OR: 1.0 (95% CI: 0.7-1.5) Glottic tumours: OR: 1.2 (95% CI: 0.8-2.0) Others : OR: 0.9 (95% CI: 0.6-1.1)	No increased risks or trends in analyses by exposure intensity or probability levels.	Elci 2003
Laryngeal cancer	Cases: 291 Washington-state residents diagnosed in 1983-87 Controls: 547 subjects selected by random-digit dialling and matched for age and sex	Occupational history collected by personal interview. Exposure assessed by a job-exposure matrix (probability and level of exposure).	Low exposure: OR: 1.0 (95% CI: 0.6-1.7) Medium exposure: OR: 1.0 (95% CI: 0.4-2.1) High exposure: OR: 2.0 (95% CI: 0.2-20) Exposure < 10 years : 0.8 (95% CI: 0.4-1.3) Exposure ≥ years: 1.3 (95% CI: 0.6-3.1)	OR adjusted for age, smoking and drinking habits and length of education.	Wortley 1992

Laryngeal cancer	Cases: 213 men with laryngeal cancers from 6 centres in Southern Europe between 1979 and 1982. Controls: 2176 age- and centre-matched controls in general population	Occupational history collected from interview. Exposure probability assessed by a panel of occupational physicians, industrial hygienists and chemical engineers.	Probable or certain exposure: OR: 1.0 (95% CI: 0.4-2.3)	OR adjusted for age, centre, alcohol, smoking, socio-economic status, diet and exposure to potential chemical confounders.	Berrino 2003
Lung cancer	Cases: 181 men (workers in plants using or manufacturing FA) who died from lung cancer between 1957 and 1979 Controls: 481 male employees in same plants	Occupational history collected from personnel records and colleagues interview. Exposure assessed by a job-exposure matrix (nature and level of exposure).	After allowance of a cancer induction period of 20 years: Duration < 5 years : OR: 1.2 (95% CI: 0.6-2.8) Duration > 5 years : OR: 0.8 (95% CI: 0.4-1.6)		Fayer-weather 1983
Lung cancer (bronchial carcinoma)	Cases: 598 men who died from lung cancer under the age of 40 years in England and Wales between 1975 and 1979 Controls: approx. 1180 controls who died from any other cause and matched for age, sex, year of death and district.	Exposure assessed by a job-exposure matrix	OR: 1.5 (95% CI: 1.2-1.8) In occupation with presumed high exposure: OR: 0.9 (95% CI: 0.6-1.4)		Coggon 1984

Lung cancer	Cases: 118 men diagnosed with lung cancer between 1957-82 and employed between 1944-65 in 35 Finnish factory using formaldehyde Controls: controls from the same cohort matched for year of birth	Exposure assessed by a job-exposure matrix	OR: 1.3 (95% CI: 0.5-3.0) OR of 0.7 after adjustment for smoking. Analysis of all cancers of the respiratory tract (lung, larynx, nasal and oral cavity and pharynx) result in not significantly elevated risk and no trend with mean level of exposure, cumulative exposure and duration of repeated exposure to peak.		Partanen 1990
Lung cancer	Cases: 308 men who died from lung cancer and from a cohort of workers employed for one year or longer in a large chemical production facility Controls: 588 controls from the same cohort matched for race, year of birth and year of hire	Exposure assessed by an industrial hygienist job-exposure matrix	OR: 0.6 (95% CI: 0.3-1.3) With a 15-year minimal latency: OR: 0.3 (95% CI: 0.1-0.9)		Bond 1986

Lung cancer	Cases: 857 Canadian men diagnosed with a lung cancer during 1979-85 Controls: 1523 men diagnosed with cancers at other sites during the same period and 533 men selected from electoral lists	Occupational history collected from interview or questionnaire. Exposure assessed by a group of chemists and hygienists (probability, intensity and frequency).	Comparison with controls with other cancer sites: < 10 years of exposure: OR: 0.8 (95% CI: 0.6-1.2) ≥ 10 years of exposure to < 0.1 ppm: OR: 0.5 (95% CI: 0.3-0.8) ≥ 10 years of exposure to 0.1-1.0 ppm: OR: 1.0 (95% CI: 0.7-1.4) ≥ 10 years of exposure to > 1 ppm: OR: 1.5 (95% CI: 0.8-2.8) Comparison with population controls: < 10 years of exposure: OR: 1.0 (95% CI: 0.6-1.8) ≥ 10 years of exposure to < 0.1 ppm: OR: 0.5 (95% CI: 0.3-0.8) ≥ 10 years of exposure to 0.1-1.0 ppm: OR: 0.9 (95% CI: 0.5-1.6) ≥ 10 years of exposure to > 1 ppm: OR: 1.0 (95% CI: 0.4-2.4)	OR adjusted for age, ethnic group, socio-economic status, cigarette smoking and various other confounding workplace exposure.	Gerin 1989
Respiratory system cancers (trachea, bronchus or lung) (Nested case-control study from the US MMVF cohort)	Cases: all (n=631) male members of the fibreglass production workers cohort who died from respiratory system cancers Controls: 570 age-matched male at-risk members of the cohort		RR: 1.61 (95% CI: 1.02-2.56) No clear trends with cumulative or average intensity of exposure. After adjustment for exposure to respirable fibres and smoking, no increased risk with cumulative exposure to FA in any of the models examined. Suggestion of increased risk with average intensity of exposure.	Relative risk adjusted for cigarette smoking	Youk 2001

Lung cancer (Nested case-control study from a cohort of workers at an iron foundry)	Cases: 220 men who died from lung cancer as an underlying or contributory cause. Controls: age- and race-matched subjects (10/case)	Assessment of exposure to formaldehyde based on a job-exposure matrix further classified as some vs none	OR=1.31 (95% CI: 0.83-2.07)	OR after adjustment for smoking, birth period and silica exposure.	Andjel-kovich 1994, 1995
Lung cancer (adenocarcino mas)	Cases: 338 men diagnosed with a lung adenocarcinomas. Controls: 1014 men hospitalised for conditions not related with smoking or recent change in diet; age-, residence and rural/urban status-matched.	Assessment of exposure to formaldehyde based on face to face interview including complete occupational history and self-reported exposure to known and suspected carcinogens.	OR=1.7 (95% CI: 1.1-2.8) based on 32 cases and 65 controls exposed to formaldehyde. 1-20 years of exposure: OR=0.9 (95% CI: 0.4-1.9) > 20 years of exposure: OR=3.0 (95% CI: 1.6-5.8) Trend: p<0.01 FA-exposed subjects were employed primarily as agricultural workers, histology technicians, medical personnel and foundry workers.	OR after adjustments for age, residence, urban/rural status, education, body mass index, smoking, number of cigerettes/year, years since quit and age at start.	De Stefani 2005
Lympho-haematopoietic malignancies	Cases: 578 leukaemia cases 622 male non-Hodgkin lymphoma cases. Controls: 1245 population-based controls age- and race-matched subjects (10/case)	Assessment of exposure to formaldehyde based occupational history	Leukaemia: OR=2.1 (95% CI: 0.4-10) (4 exposed cases) Acute ML: OR=6.7 (95% CI: 1.2-36) (3 exposed cases) Non-Hodgkin lymphoma : OR=3.2 (95% CI: 0.8-13) (6 exposed cases) Follicular non-Hodgkin lymphoma : OR=6.7 (95% CI: 1.2-37) (3 exposed cases)	OR among subjects employed in funeral homes and crematoria	Linos 1990

Lympho-haematopoietic malignancies	Cases: 53 Canadian men diagnosed with a Hodgkin lymphoma and 206 with non-Hodgkin lymphoma during 1979-85 Controls: 533 men selected from electoral lists	Occupational history collected from interview or questionnaire. Exposure assessed by a group of chemists and hygienists (probability, intensity and frequency).	Non-Hodgkin lymphoma: < 10 years of exposure: OR: 0.7 (95% CI: 0.3-1.6) ≥ 10 years of exposure to < 0.1 ppm: OR: 1.1 (95% CI: 0.5-2.2) ≥ 10 years of exposure to 0.1-1.0 ppm: OR: 1.0 (95% CI: 0.5-2.1) ≥ 10 years of exposure to > 1 ppm: OR: 0.5 (95% CI: 0.1-1.7) Hodgkin lymphoma: Exposed cases : OR: 0.5 (95% CI: 0.2-1.4)	OR adjusted for age, ethnic group, socio-economic status, cigarette smoking and various other confounding workplace exposure.	Gerin 1989
Lympho-haematopoietic malignancies	Cases: 12 men diagnosed with leukaemia, 4 with Hodgkin's disease and 8 with non Hodgkin's lymphoma between 1957-82 and employed between 1944-65 in the Finnish wood industry Controls: 79, 21 and 52 controls, respectively, from the same cohort matched for year of birth and vital status.	Exposure assessed by a job-exposure matrix	OR compared with subjects with cumulative exposure less than 3 ppm-months. Leukaemia: OR: 1.40 (95% CI: 0.25-7.91) Hodgkin's disease: not applicable. Only 1 exposed case Non Hodgkin's lymphoma: OR: 4.24 (95% CI: 0.68-26.6)		Partanen 1993

Lympho-haematopoietic malignancies	Cases: 400 patients diagnosed with myelodysplastic syndrome in UK Controls: cancer-free controls matched for age, sex, area of residence and hospital and year of diagnosis	Occupational history, duration and intensity of exposure collected from interview.	Myelodysplastic syndrome : ≥ 10 h lifetime exposure vs others: OR: 1.17 (95% CI: 0.51-2.68) ≥ 50 h lifetime exposure vs others: OR: 2.33 (95% CI: 0.55-11.35) ≥ 2500 h lifetime exposure vs others: OR: 2.0 (95% CI: 0.32-15.67)		West 1995
Lympho-haematopoietic malignancies	Cases: 185 US patients diagnosed with small-cell diffuse lymphoma, 268 with follicular lymphoma, and 526 with large-cell diffuse lymphoma between 1984-88 Controls: 1659 controls selected by random-digit dialling and matched for age and area of diagnosis	Background characteristics, occupational and military history collected from telephone interview.	Ever vs never exposed: Small-cell diffuse lymphoma: OR: 1.40 (95% CI: 0.87-2.40) Follicular lymphoma: OR: 0.71 (95% CI: 0.41-1.20) Large-cell diffuse lymphoma : OR: 1.10 (95% CI: 0.79-1.70) All cases of non-Hodgkin lymphoma : OR: 1.20 (95% CI: 0.86-1.50)	OR adjusted for age, ethnic group, socio-economic status, education, religion, Vietnam participation and cigarette smoking.	Tatham 1997

Lympho-haematopoietic malignancies	Cases: 340 US patients diagnosed with leukaemia (214 chronic lymphocytic, 13 acute lymphocytic, 46 chronic myeloid and 132 acute myeloid leukaemia) and 58 myelodysplasia Controls: 1087 controls selected by random-digit dialling and matched for age, vital status and area of residence	Occupational history collected from interview. Exposure assessed by an industrial hygienist (probability and intensity).	Leukaemia: CLL: Low-medium: OR: 1.2 (95% CI: 0.7-1.8) High: OR: 0.6 (95% CI: 0.1-5.3) ALL: none of the cases was exposed CML: Low-medium: OR: 1.3 (95% CI: 0.6-3.1) High: OR: 2.9 (95% CI: 0.3-24.5) AML: Low-medium: OR: 0.9 (95% CI: 0.5-1.6) High: no cases Myelodysplasia: Low-medium: OR: 0.8 (95% CI: 0.3-1.9) High: no cases All leukaemia and myelodysplasia: Low-medium: OR: 1.0 (95% CI: 0.7-1.4) High: OR: 0.7 (95% CI: 0.2-2.6)	OR adjusted for education, cigarette smoking, use of hair dyes and first degree relative with a haematopoietic tumour and compared with no exposure.	Blair 2001

Lympho-haematopoietic malignancies Non-Hodgkin lymphoma (NHL)	Cases: 601 women from Connecticut diagnosed with NHL Controls: 717 women from Connecticut selected by random-digit dialling and matched for age.	Occupational history collected from interview. Exposure assessed with a job-exposure matrix.	Never vs ever exposed: OR: 1.3 (95% CI: 1.0-1.7) Never exposed vs intensity of exposure: Low: OR: 1.4 (95% CI: 1.0-1.8) Medium: OR: 1.2 (95% CI: 0.8-1.7) p for trend =0.21 Never exposed vs average exposure probability: Low: OR: 1.3 (95% CI: 1.0-1.7) Medium: OR: 1.4 (95% CI: 0.9-2.3) p for trend =0.11 Never vs ever exposed by subtype: Diffuse large B-cell lymphoma: OR: 1.9 (95% CI: 1.3-2.6) Follicular lymphoma: OR: 1.1 (95% CI: 0.7-1.6) Chronic lymphocytic leukaemia/small lymphocytic lymphoma: OR: 1.2 (95% CI: 0.7-2.0)	OR adjusted for age, family history of hematopoietic cancers, alcohol consumption and race. No influence of education, income, cigarette smoking on results.	Wang 2009b

Lympho-haematopoietic malignancies			Lymphoid origin: No embalming: OR: 1.0 Embalming: OR: 1.1 (95% CI: 0.5-2.1) Nonlymphoid origin: No embalming: OR: 1.0 Embalming: **OR: 3.0 (95% CI: 1.0-9.5)** Myeloid leukaemia: No embalming: OR: 1.0 Embalming: **OR: 11.2 (95% CI: 1.3-95.6)**	OR adjusted for year of birth, age at death, sex, data source and smoking status. Significant trends were observed with increasing years of embalming practice (p=0.046 for nonlymphoid origin and p=0.020 for myeloid leukaemia) and peak exposure (p=0.036 for myeloid leukaemia) but not for cumulative exposure and average intensity while embalming.	Hauptmann 2009

Brain cancer	Cases: 48 deceased funeral directors and embalmers with brain tumour identified as cause of death. Controls: 265 individuals in the funeral industry with other cause of death and matched for age, sex and date of death. Cases and controls were part of the cohorts of Hayes 1990, Walrath 1983 or Walrath 1984.	Information on work practice and demographic characteristics were obtained by interview of one next to kin and several coworkers per subjects. Questionnaire responses were linked to a predictive model based on exposure-assessment data.	No embalming: OR: 1.0 Embalming: OR: 1.9 (95% CI: 0.7-5.3)	OR adjusted for year of birth, age at death, sex, data source and smoking status. No significant trends observed with increasing years of embalming practice, peak exposure, cumulative exposure or average intensity while embalming.	Hauptmann 2009
Bladder cancer	Cases: 484 Canadian men diagnosed with a bladder cancer during 1979-85 Controls: 1879 men diagnosed with cancers at other sites during the same period and 533 men selected from electoral lists	Occupational history collected from interview or questionnaire. Exposure assessed by a group of chemists and hygienists (probability, intensity and frequency).	Non-substantial exposure: OR: 1.2 (95% CI: 0.9-1.8) Substantial exposure: OR: 0.9 (95% CI: 0.5-1.7)	OR adjusted for age, ethnic group, socio-economic status, cigarette smoking and various other confounding workplace exposure.	Siemiatycki 1994

Rectal cancer	Cases: 257 Canadian men diagnosed with rectal cancer during 1979-85 Controls: 1295 men diagnosed with cancers at other sites during the same period	Occupational history collected from interview or questionnaire. Exposure assessed by a group of chemists and hygienists (probability, intensity and frequency).	Non-substantial exposure: OR: 1.2 (95% CI: 0.8-1.9) Substantial exposure: OR: 2.4 (95% CI: 1.2-4.7) Increasing risk with increasing concentration and duration of exposure.	OR adjusted for age, education, cigarette smoking, beer consumption and body mass index. Many substances showed association with rectal cancer and it was not possible to identify the independent effect of these substances.	Dumas 2000
Uveal melanoma	Cases: 221 white men diagnosed with uveal melanoma in San Francisco during 1978-87 Controls: 447 white men selected by random-digit dialling and matched for age	Chemical exposure determined from interview. Exposure assessed by a group of chemists and hygienists (probability, intensity and frequency).	OR: 2.9 (95% CI: 1.2-7.0)	OR adjusted for potential occupational and non-occupational confounder and comparing ever to never exposed.	Holly 1996

Oesophageal cancer (squamous cell carcinoma)	Cases: 122 men with oesophageal cancer diagnosed between 1988 and 1991 in two Swedish regions Controls: 641 men matched for age and location	Occupational history collected from interview and structured questionnaire. Exposure assessed by an industrial hygienist (probability and intensity).	RR=1.90 (95% CI: 0.99-3.63) based on 19 exposed cases. No dose-response trend based on cumulative dose or duration of exposure.	RR adjusted for region, age, alcohol intake and tabacco smoking.	Gustavs-son 1998
Pancreatic cancer	Cases: 63097 subjects who died from pancreatic cancer between 1984 and 1993 in 24 US states Controls: 252386 age-, race-, gender- and state-matched subjects who died from other cancers	Usual occupation was obtained by death certificate. Probability and intensity of exposure to formaldehyde and numerous solvents was assessed by a job-exposure matrix	Low probability: OR: 1.2 (95% CI: 1.1-1.3) Medium probability: OR: 1.2 (95% CI: 1.1-1.3) High probability: OR: 1.4 (95% CI: 1.2-1.6) Low intensity: OR: 1.2 (95% CI: 1.1-1.3) Medium intensity: OR: 1.2 (95% CI: 1.1-1.3) High intensity: OR: 1.1 (95% CI: 1.0-1.3)		Kernan 1999
Thyroïd cancer	Cases: 130 women with thyroid cancer between 1989 and 1998 from a cohort of 267 400 women working in one of 526 textile factories in Shanghai, China in 1989 Controls: 3 187 women from same cohort, randomly selected and matched for age.	Job history was obtained from factory documents and a job-exposure matrix was used. Exposure was based on a combination of historical monitoring, factory inspection reports and literature.	Age-adjusted hazard ratio of exposed for various duration vs never exposed: < 10 years: no cases ≥ 10 years: 8.33 (95% CI: 1.16-60)		Wong 2006

4.10.2.4 Meta-analysis

Table 22: Meta-analysis

Cancer site	Selected studies	Estimation of exposure	End-point	Result	Observations and remarks	Ref
Respiratory cancers	35 cohort and case-control studies (men only)	Exposure was categorised as low/medium for any exposure up to 5.5 ppm-year and substantial for exposure exceeding 5.5 ppm-year.	Nasopharynx: Nasal cavity and paranasal sinuses: Lung cancer: Other respiratory cancers:	Low/medium exposure: RR=1.6 (95% CI: 1.0-2.7) **Substantial exposure: RR=2.7 (95% CI: 1.4-5.6)** Low/medium exposure: RR=1.1 (95% CI: 0.7-1.8) **Substantial exposure : RR=1.7 (95% CI: 1.0-2.8)** **Low/medium exposure: RR=1.2 (95% CI: 1.1-1.3)** Substantial exposure : RR=1.1 (95% CI: 1.0-1.2) Low/medium exposure: RR=1.1 (95% CI: 0.7-1.5) Substantial exposure : RR=1.2 (95% CI: 0.6-2.1)		Partanen 1993

Upper respiratory cancers	6 industrial cohort, 8 medical specialists and embalmers cohort and 18 case-control studies	Average exposure was assessed for 33 different job classes	<u>Lung cancer</u> All studies (n=24) Industrial cohort Pathologist cohort Embalmer cohort Nested case-control Non-nested case-control <u>Nasal cancer</u> All studies (n=20) Industrial cohort Other cohorts Case-control US case-control European case-control <u>Nasopharynx cancer</u> All studies (n=12) All cohorts Industrial cohort All case-control	MRR: 1.0 (95% CI: 0.9-1.0), p-value for heterogeneity<0.00001 MRR=1.1 (95% CI: 1.0-1.2), p=0.91 MRR=0.5 (95% CI: 0.4-0.6), p=0.009 MRR=1.0 (95% CI: 0.9-1.1), p=0.82 MMR=0.7 (95% CI: 0.4-1.1), p=0.94 MMR=0.8 (95% CI: 0.7-1.0), p=0.50 MRR: 1.0 (95% CI: 1.0-1.1) MRR=0.6 (95% CI: 0.1-1.7) MRR=0.0 (95% CI: 0.0-1.6) **MRR=1.8 (95% CI: 1.4-2.3), p=0.0001** MMR=1.0 (95% CI: 0.7-1.5), p=0.17 **MMR=2.9 (95% CI: 2.2-4.0), p=0.06** **MRR: 1.3 (95% CI: 1.2-1.5)** MRR=1.0 (95% CI: 0.5-1.8) MRR=1.2 (95% CI: 0.4-2.5) MRR=1.3 (95% CI: 0.9-2.1), p=0.08	Lung cancer: no excess of risk with a high homogeneity in industrial and embalmer cohort as well as nested case-control studies. Nasal cancer: no increase of risk in all studies and deficit in mortality in cohort studies (not significant). Increase of mortality in case-control studies mainly explained by European studies results and with substantial heterogeneity. Nasopharyngeal cancer: moderate increase of cancer risk. Case-control studies gave slightly more elevated risk than cohort studies although they represent lower and less certain exposure.	Collins 1997
Nasopharyngeal cancer	8 cohort studies and 7 case-control studies published through May 2009		<u>Cohort studies :</u> Overall NPC (n=7) Location - not adjusted (n=5)	 RR= 0.72 (95% CI: 0.40-1.29) RR=0.74 (95% CI: 0.39-1.40)	All primary cohort study results entirely or partly based on plant 1 of the NCI cohort were not included in the meta-analysis. Overall Q-test	Bachand 2010

	(PMR studies not included)		- adjusted (n=2) <u>Case-control studies :</u> Overall NPC (n=6) Socioeconomic status - not adjusted (n=3) - adjusted (n=3) Smoking - not adjusted (n=2) - adjusted (n=4) Location - not adjusted (n=3) - adjusted (n=3)	RR=0.61 (95% CI: 0.14-2.58) RR= 1.22 (95% CI: 1.00-1.50) RR=1.23 (95% CI: 0.93-1.62) RR=1.22 (95% CI: 0.91-1.63) RR=1.32 (95% CI: 1.01-1.71) RR=1.10 (95% CI: 0.80-1.51) RR=1.16 (95% CI: 0.88-1.54) RR=1.29 (95% CI: 0.96-1.73)	*p* value was 0.924 suggesting homogeneity among cohort studies. When data from plant 1 were included (Marsh 2005) the overall risk estimate increased from 0.72 to 1.60. The overall Q-test p value was <0.0001, indicating that inclusion of plant 1 led to significant heterogeneity among studies. The case-control NCI re-analysis from Marsh 2007a entirely based on plant 1 was excluded from results. Its inclusion had any effect on the results (result not shown). Overall Q-test *p* value was 0.705 suggesting homogeneity among case-control studies. No evidence of heterogeneity was observed within any subgroup of case-control studies.	

Various cancers	32 cohort and case-control studies including 14 with professional exposure and 18 with industrial exposure cohorts		Lung:	Professional : **RR=0.9, p<0.05** (511 cases vs 583.8 expected) Industrial : **RR=1.1, p<0.05** (1181 cases vs 1096.8 expected)	No association with latency of exposure.	Blair 1990b
			Nasal cavity:	Professional : RR=0.4 (1 cases vs 2.4 expected) Industrial : RR=1.1 (60 cases vs 56.0 expected)	No association with level or duration of exposure.	
			Nasopharynx:	Professional : RR=2.2 (4 cases vs 1.8 expected) Industrial : RR=1.2 (31 cases vs 25.4 expected)	A statistical significant trend with level or duration of exposure was observed.	
			Leukaemia:	Professional : **RR=1.6, p<0.05** (107 cases vs 67.0 expected) Industrial : RR=1.1 (122 cases vs 114.4 expected)		
			Hodgkin's disease:	Professional : RR=0.5 (6 cases vs 11.5 expected) Industrial : RR=0.8 (22 cases vs 26.0 expected)		
			Brain:	Professional : **RR=1.5, p<0.05** (60 cases vs 41.0 expected) Industrial : RR=0.9 (111 cases vs 129.1 expected)		
			Colon:	Professional : **RR=1.3, p<0.05** (206 cases vs 155.7 expected) Industrial : RR=0.9 (228 cases vs 257.7 expected)		

Various cancers	12 cohorts published through February 2007		Oral cavity and pharynx: Lung: Brain: Lymphatic and hemopoietic: Leukaemia:	Ind. workers: RR=1.09 (95% CI: 0.88-1.34) Professionals: RR= 0.96 (95% CI : 0.75-1.24) Ind. workers: RR=1.06 (95% CI: 0.92-1.23) Professionals: RR= 0.63 (95% CI : 0.47-0.84) Ind. workers: RR=0.92 (95% CI: 0.75-1.13) Professionals: **RR= 1.56 (95% CI : 1.24-1.96**) Ind. workers: RR=0.85 (95% CI: 0.74-0.96) Professionals: **RR= 1.31 (95% CI : 1.16-1.48)** Ind. workers: RR=0.90 (95% CI: 0.75-1.07) Professionals: **RR= 1.39 (95% CI : 1.15-1.68)**	For nasopharynx a SMR of 1.33 (0.61-2.53) is calculated in 3 cohorts of industrial workers. Excluding a cluster of 6 deaths from a single plant of the NCI study, the pooled RRamong industry declined to 0.49 based on 3 deaths. For the sinus and nasal cavity, a SMR of 1.01 (0.33-2.35) is calculated in 3 cohorts of industrial workers. No death was observed in professionals.	Bosetti 2008

Leukaemia	13 case-control studies and 1 nested case-cohort study		<u>Leukaemia (all studies)</u> <u>Myeloid leukaemia</u> <u>Leukaemia - High exposure</u> <u>Professional workers</u> <u>Industry workers</u> <u>Industry workers (high exposure)</u>	**RR= 1.53 (95% CI: 1.11-2.11)** **RR=2.47 (95% CI: 1.42-4.27)** **RR=1.55 (95% CI: 1.04-2.31)** **RR=2.27 (95% CI: 1.15-4.45)** RR=1.38 (95% CI: 0.96-1.99) RR=1.45 (95% CI: 0.95-2.22)	When RR estimates for different levels of exposure were provided, the RR for the highest level was used in the meta-analysis for each study included in the meta-analysis. Indeed, if a true relationship exists, higher RR are expected in higher exposure groups and will have greater statistical power. Sensitivity analyses were done to evaluate the impact of the excluded studies. No significant effect was observed on RR estimates. It is noted that in the sub-population of R&D workers from the study by Dell *et al* (1995) included in the meta-analysis (accouting for 11.4% of the meta-analysis), there was no obvious common exposure (including FA) except to solvents including toluene and benzene.	Schwilk 2010 (update of Zhang 2009)

Leukaemia	15 cohort studies and 2 case-control studies published through May 2009 (PMR studies excluded)		<u>Cohort studies:</u> Leukaemia (n=15) Myeloid (n=3) Lymphatic/lymphocytic (n=2) Other (n=2) Professional (n=7) Industrial (n=8) US/Canada (n=11) Europe (n=4) <u>Case-control studies:</u>	 RR= 1.05 (95% CI: 0.93-1.20) RR=1.09 (95% CI: 0.84-1.40) RR=1.11 (95% CI: 0.81-1.52) RR=0.97 (95% CI : 0.71-1.33) RR=1.28 (95% CI: 0.98-1.66) RR=0.99 (95% CI: 0.86-1.15) RR=1.05 (95% CI: 0.92-1.20) RR=1.10 (95% CI: 0.43-2.77) OR : 0.99 (95% CI : 0.71-1.37)	Overall Q-test *p* value was 0.928 suggesting homogeneity among cohort studies. No evidence of heterogeneity was found among studies within any subgroup.	Bachand 2010
Hematologic cancers	15 case-control and cohort studies that provide relative risk estimate of haematological malignancies associated with high occupational exposure		Lympho-hematopoietic (all) Leukaemia (all) Myeloid leukaemia Hodgkin lymphoma Non-Hodgkin lymph. Multiple myeloma	**RR= 1.25 (95% CI: 1.09-1.43)** **RR=1.54 (95% CI: 1.18-2.00)** **RR=1.90 (95% CI: 1.31-2.76)** RR=1.23 (95% CI : 0.67-2.29) RR=1.08 (95% CI: 0.86-1.35) RR=**1.31 (95% CI: 1.02-1.67)**	Highest exposure groups from each study were included in the meta-analysis. When several exposure metrics were available, one RR was selected in the following order: peak, average intensity, cumulative exposure or duration. Results were adjusted for heterogeneity when present.	Zhang 2009

Leukaemia	12 cohort mortality studies, 2 case-control studies and 4 proportionate mortality or incidence studies published from 1975 to 2003		All studies = 287 leukaemias US and Canadian workers European workers Industrial workers Embalmers Pathologists and anatomists	Meta-relative risk: 1.1 (95% CI: 1.0-1.2), p-value for heterogeneity = 0.07 MRR=1.2 (95% CI: 1.0-1.4), p=0.07 MRR=0.9 (95% CI: 0.7-1.1), p=0.69 MRR=0.9 (95% CI: 0.8-1.0), p=0.35 MMR=1.6 (95% CI: 1.2-2.0), p=0.97 MMR=1.4 (95% CI: 1.0-1.9), p=0.96	Small but consistent increase in leukaemia risk in embalmers, pathologists and anatomists but not in industrial workers with presumed higher average and peak exposure. Confounding with smoking appears unlikely as embalmers, pathologists and anatomists have low rates of lung cancer. Better diagnostic procedures given professions and socio-economic status may increase leukaemia death rates.	Collins 2004

Pancreatic cancer	8 cohort mortality studies, 2 case-control studies and 4 proportionate mortality or incidence studies published between 1983 and 1999	Estimated formaldehyde exposure: Anatomists /pathologists: TWA=0.35 ppm; peak=4.1 ppm Embalmer: TWA=0.15 ppm; peak=5.5 ppm Industrial workers: TWA=3.2 ppm; peak=10 ppm	All studies = 364 pancreatic cancers US and Canadian workers European workers Industrial workers Embalmers Pathologists and anatomists	Meta-relative risk: 1.1 (95% CI: 1.0-1.2), p-value for heterogeneity = 0.12 MRR=1.2 (95% CI: 1.0-1.3), p=0.10 MRR=1.0 (95% CI: 0.8-1.2), p=0.49 MRR=0.9 (95% CI: 0.8-1.1), p=0.38 MMR=1.3 (95% CI: 1.0-1.6), p=0.90 MMR=1.3 (95% CI: 1.0-1.7), p=0.30	Small increase in pancreatic cancer risk in embalmers, pathologists and anatomists but not in industrial workers with higher average and peak exposure. Suggests no relationship between pancreatic cancer and FA exposure.	Collins 2001

Pancreatic cancer	92 studies representing 161 different exposed populations. Five populations were exposed to formaldehyde.	Different sources of exposure data.	All 5 populations Men Unspecified or both Histo. Diagnosis No histo. diagnosis Case-control and cohort studies with internal reference SMR/SIR studies	Meta-relative risk: 0.8 (95% CI: 0.5-1.0), p-value for heterogeneity = 0.3 MRR=0.8 (95% CI: 0.5-1.3) MRR=0.6 (95% CI: 0.3-1.1) MMR=0.5 (95% CI: 0.3-0.9) MMR=0.9 (95% CI: 0.7-1.3) MRR=0.5 (95% CI: 0.3-1.6) MRR=0.9 (95% CI: 0.7-1.3)		Ojajarvi 2000

4.10.3 Other relevant information

Table 23: Other relevant experimental studies in the context of assessment of carcinogenic potential of formaldehyde

Species	Conc. mg/ m^3	Expo. time (h/day)	Durat° of treatm^t	Observations and Remarks	Ref.
F-344 male rats (n=8/group) (test substance: FA 10.21% in water)	0, 0.6, 1.25, 2.49, 7.5, 12.5, 19 mg/ m^3 (0, 0.5, 1, 2, 6, 10, 15 ppm)	6h/d 5d/wk (whole-body)	4 wk	NALT and cervical lymph nodes were examined. In the NALT, the following effects were reported: - Tendancy to a decreased size - 1 animal with decreased cellularity at 2 ppm and 3 at 15 ppm - Tendancy to an increased number of animals with absence of germinal centre development (0 at 15 ppm vs 1 with very slight and 3 with slight development in controls) - Slight to moderate hyperplasia of the lymphoepithelium at 15 ppm - Increased cell proliferation in the epithelium at 15 ppm - No significant change in cell proliferation in the other compartments despite low counts at 15 ppm in the follicular area. In the cervical lymph nodes: - Increased number of animals with absence of germinal centre development (0 at 15 ppm and 2 ppm vs 5 with very slight development in controls) - No effect on cell proliferation. The author concluded that the only distinct finding was hyperplasia in the NALT lymphoepithelium at 15 ppm.	Kuper 2011
B6C3F1 female mice (n=6/group)	0, 0.6, 1.25, 2.49, 7.5, 12.5, 19 mg/ m^3 (0, 0.5, 1, 2, 6,	6h/d 5d/wk	4 wk	No effect detected in NALT and cervical lymph nodes.	Kuper 2011

(test substance: FA 10.21% in water)	10, 15 ppm)	(whole -body)			

Table 24: Other relevant human studies in the context of assessment of carcinogenic potential of formaldehyde

Test	Population	Exposure	Observations and remarks	Ref
Effect of formaldehyde on lympho-haemato-poietic system	Exposed : 50 hemodialysis nurses from 4 Taiwanese hospitals where dialiser are sterilised with formaldehyde. Sodium perchlorate was also used during dialysis. Controls : 71 nurses from same hospitals working in other units;	Exposure was tested according to NIOSH protocol. Mean personal sampling range from 0.015 to 0.054 ppm in the different hospitals (highest level: 0.089 ppm) and mean area sampling from 0.006 to 0.237 ppm (highest level: 2.80 ppm)	The exposure groups was found to have significantly increased incidence of dizziness, nausea, difficulty concentrating, tearing, nasal discharge, cough and difficulty breathing. No association was found between FA exposure and blood analysis in the first blood count analysis. Formaldehyde level and symptom scores were correlated with lower WBC in the second blood count analysis one year later. No other blood count parameter displayed a positive correlation with FA exposure.	Kuo 1997

Effect of formaldehyde on lympho-haemato-poietic system	Exposed: 43 workers exposed to FA concentration between 0.6 and 2.5 ppm daily for at least 3 months in a factory producing FA-melanine resins and one factory using resins in China. Controls: 51 unexposed workers from the same geographic region with comparable demographic and socioeconomic characteristics, matched by age and gender. Exposed and controls subjects were not exposed to benzene, radiation or other known hematotoxic agents	Occupational exposure collected by a questionnaire administered by a trained interview. Exposure was monitored for a full shift on 3 working days for each subject. Median exposure concentration: 1.28 ppm (10^{th} percentile: 0.63 ppm; 90^{th} percentile: 2.51 ppm) in exposed subject	Total white blood cell counts were significantly lower in workers exposed to FA compared to controls (5.422±1.529 vs 6.269±1.422, p=0.0016). Lower levels were observed for all major myeloid cell types. It is however noted that the observed variations are in the range of normal values. A 20% decrease in colony formation from progenitor cells was observed in the FA-exposed workers but this was not statistically significant (p=0.10). *In vitro* culture of human blood progenitor cells from a volunteer in presence of formaldehyde (0 to 200 µM) showed a dose-related decrease in formation of colony indicating that FA inhibits proliferation of myeloid progenitor cells.	Zhang 2010

4.10.4 Summary and discussion of carcinogenicity

Animal data

Further to administration of formaldehyde in drinking water in Wistar rats, an increase of squamous cell papillomas in the forestomach was seen in Takahashi 1986 in spite of the short duration of exposure (32 weeks). Induction of tumours in the gastrointestinal tract was however not reproduced in Til 1989 and in Tobe 1989 at similar high doses and in presence of severe irritation of the gastrointestinal tract. Til 1989 was performed on high number of animals in accordance to current carcinogenicity guideline and is considered to be the best study to evaluate carcinogenicity of formaldehyde by oral route. The induction of benign tumours in the forestomach in Takahashi 1986 is therefore considered equivoqual.

In these three studies, no increase in lymphohaematopoietic malignancies was reported.

Soffritti et al. (1989) report an increased incidence in lymphohaematopoietic malignancies and cases of rare gastrointestinal tumours in Sprague-Dawley rats. An increased incidence of testicular interstitial adenomas was also reported in the most recent publication (Soffritti 2002). However, several criticisms have been raised on this study: the various lymphohaematopoietic malignancies were pooled in the analysis so that incidence for each subtype is not available and significance of the finding is therefore unclear. Besides, important discrepancies were noted between the two publications that report the same study results and the studies are therefore not considered reliable.

Overall, no convincing evidence of a carcinogenic effect of formaldehyde via oral route is available.

Via dermal exposure, three promotion studies were inconclusive. They did not report an increase of tumours but their limited duration of exposure and number of animals exposed and their focus on skin tumours raise doubts on the validity of the studies in the assessment of the carcinogenic potential of formaldehyde by dermal route.

Overall, no convincing evidence of a carcinogenic effect of formaldehyde via dermal route is available.

Inhalation of FA consistently induces nasal squamous cell carcinomas in rats as summarised in Table. 24. Two studies were not considered of sufficient validity and were not included in the table: Holmström et al. (1989) reporting 6% of squamous cell carcinoma at 12.4 ppm, because of its small number of animals (n=16/group) and Feron et al. (1988) because of its short duration of exposure (13 weeks). No malignant tumours were observed at doses equivalent or lower to 2 ppm but a steep non-linear increase in incidence is seen from 5.6 ppm in most studies. Signs of inflammation and non-neoplasic proliferation in the nasal cavity are also observed in all studies from 2 ppm.

Table 25. Incidence of tumours and precursor lesions in the nasal cavity of rats following inhalation

Dose (ppm)	**0.1** [a]	**0.3** [b]	**0.7** [c]	**1** [a]	**2** [c]	**2** [b]	**2** [d]	**5.6** [d]	**6** [c]	**10** [a]	**10** [c]	**14.2** [e]	**14.3**[d]	**15** [b]	**15** [c]
Squamous cell carcinomas (%)	0	0	0	0	0	0	0	0.8	1	4	22	38	44	41	47
Other malignant tumours* (%)	0	0	0	0	0	0	0	0	0	0	2	2	2	3	1.4
Polyps, papillomas or polypoid adenomas (%)	0	0	0	0	0	0	3	2.6	0	0	5.6	10	2	9	9.5
Signs of chronic irritation															
Epithelial cell yperplasia	-	+	-	-	-	+	-	-	-	+	+	-	+	+	+
Epithelial dysplasia	NR	NR	-	NR	NR	NR	+	+	NR	NR	NR	NR	+	NR	NR
Squamous cell metaplasia	-	+	-	-	-	+	+	+	+	+	+	+	+	NR	+
Rhinitis	-	-	-	-	-	+	+	+	NR	+	NR	-	+	+	NR
Cell infiltration	NR	-	-	NR	-	-	NR	NR	NR	NR	+	NR	NR	-	+
Edema	NR	-	-	NR	-	-	NR	NR	NR	NR	NR	NR	NR	-	NR

[a] Woutersen 1989; [b] Kamata 1997; [c] Monticello 1996; [d] Kerns 1983; [e] Sellakumar 1985; * carcinoma, carcinosarcoma, fibrosarcoma, rhabdomyosarcoma; +: sign reported as present; -; sign reported as absent; NR: not reported

In all studies in mice, no nasal tumours were reported in controls except 1 polyploid adenoma (0.4%) in Kerns 1983.

In this study (Kerns 1983) reports a small non-significant increase in nasal squamous cell carcinomas (2%) at the highest dose in males only (14.3 ppm). This tumour was however not observed in any other control or treated animals. Inflammation of the nasal mucosa including squamous metaplasia was also observed from 5.6 ppm and this study suggests a lower sensitivity to FA-induced irritation and nasal tumour induction in this species.

In hamsters, no tumours of the respiratory tract were produced up to 10 ppm and only minimal hyperplasia and metaplasia were observed.

No evidence of induction of tumours at distant sites and in particular in the lymphohaematopoietic system was obtained by inhalation.

<u>Overall,</u> the carcinogenicity of formaldehyde is well established in rats by inhalation with induction of tumours at the site of contact. Formaldehyde is highly cytotoxic and irritant and nasal tumours are observed only at doses producing chronic irritation as evidenced by the accompanying inflammatory, hyperplastic and metaplastic responses. Among species, the degree of sensitivity to nasal irritation is associated with the degree of sensitivity to nasal tumour induction. Localisation of damage to the nasal epithelium also corresponds with tumour site and distribution is attributable to regional dosimetry and/or local tissue susceptibility.

A consistent database provides evidence that regenerative cell on (RCP) secondary to cytolethality highly correlates with tumour incidence and regional distribution. RCP is observed at 10 and 15 ppm with 6 ppm being a borderline concentration (Monticello 1996, Casanova 1994, Meng 2010). Besides, Woutersen et al. (1989) have demonstrated that nasal mucosa damage induced by preexposure electrocoagulation treatment contributes to tumour induction.

Modeling studies (Conolly 2004) have discussed induction of proliferation in response to cytotoxicity and formation of DPX to explain the mechanism of nasal tumour induction and its particular dose-response relationship.

At low dose, a delay in replication by DPX formation may induce a decrease in cellular proliferation as supported by the observed J-shape dose-response (Conolly 2004) and is it may allow the repair of DNA damages. A delay in cell replication at low dose was however not confirmed by the findings of Meng *et al.* (2010) observing a dose-related increase in cell proliferation significant from 10 ppm. As discussed in the mutagenicity part, at low dose the incremental DNA damage may therefore be repaired due to non-elevated levels in cell proliferation and the genotoxic potential of formaldehyde is not expected to give rise to mutagenicity at low doses.

At higher dose, cytolethality is followed by a RCP. An increased rate in cell proliferation is associated with a larger probability of fixing a primary DNA lesion as a mutation and a decrease in the time available for DNA repair. Observation of hyperplastic and metaplastic changes strongly support the hypothesis of a mechanism driven by regenerative proliferation accompanied by an inflammatory response that may also secondary amplify the high-dose genotoxic effects of formaldehyde. A steep increase in tumour induction is therefore expected at doses exerting cytotoxicity and RCP as observed experimentally. It is also consistent with the induction of chromosomal aberrations at the site of contact at high dose in Dallas et al. (1992). Besides, saturation of the glutathione mediated detoxification of FA may contribute to the non linearity of the dose response (2007)

Experimental results and mechanistic data therefore support the existence of a threshold type dose-response for induction of nasal tumours with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role above this threshold.

Overall, there is no convincing evidence of a carcinogenic effect at distant sites or via other routes of exposure than inhalation.

Human data

Numerous studies investigate the association of formaldehyde exposure with cancer incidence. They consist of cohorts, case-control studies and meta-analyses. In all these studies, human exposure was by inhalation.

Cohorts report mortality or incidence of cancers in two types of exposed workers: industrial cohorts from formaldehyde production plants, resin plants or other industries using formaldehyde or professional cohorts of embalmers or anatomo-pathologists. Three large, recently-updated industrial cohorts are considered as the most informative: the NCI cohort (Beane-Freeman 2009 and Hauptmann 2004), the British cohort (Coggon 2003) and the NIOSH cohort (Pinkerton 2004) include large populations and provide detailed assessments of the levels of exposure. It should be noted that among these cohorts, exposure was lower in the NIOSH cohort with limited exposure to peaks. Exposure characteristics are summarised in Table 26 below.

Table 26 Exposure characteristics of the three main occupational cohorts

	NCI cohort[1]	British cohort (Coggon 2003)[2]	NIOSH cohort[3]
Size of the cohort	n=25619	n=14014	n= 11039
Average exposure	Median TWA-8hr = 0.3 ppm (range: 0.01-4.3 ppm) 3927 subjects (15%) with TWA ≥ 1 ppm	3872 subjects (28% with exposure < 0.1 ppm; 3815 subjects (27%) with exposure 0.1-0.5 ppm; 1362 (10%) with exposure 0.6-2 ppm; 3993 (28%) with exposure > 2 ppm; 975 (7%) with unknown exposure.	Mean TWA-8hr = 0.15 ppm (range: 0.09-2.0 ppm)
Peak exposure	6255 subjects (24%) exposed to peaks ≥ 4 ppm	No data	Continuous air monitoring suggested no substantial peaks.

[1] Based on data from Beane-Freeman 2009; [2] Based on data from Gardner 1993; [3] Based on data from Pinkerton 2004

The other industrial cohorts available are generally not focused on formaldehyde except Bertazzi *et al.* (1989) and Hansen *et al.* (1995). They consist of smaller cohorts with fewer or unknown (Wesseling 2002) number of people exposed to formaldehyde. Exposure to formaldehyde was also generally lower and/or less adequately characterised.

None of the professional cohorts available investigate characterisation and analysis of levels of exposure. The mean concentrations of formaldehyde in the workroom of mortuaries, hospitals and laboratories reported in the IARC review (2006) range from 0.05 to 4.2 ppm and embalmers and anatomists are expected to be exposed to higher peaks than in industrial settings. Among the professional cohorts, the British pathologist cohort (Hall 1991) and the US embalmer cohort (Hayes 1990) include the largest population.

Epidemiological data showing a positive association are summarised in table 27 below. Epidemiological data are then discussed below for each potential site of cancer.
In the overall weight of evidence, it is considered that studies showing a statistically significant excess of risk supported by statistically significant trends with one exposure metrics (when evaluated) provide the strongest level of evidence that the observed carcinogenic effects is related to formaldehyde exposure. In addition to the studies reporting statistically significant excess of risk (with or without trends with exposure) the studies with a non-statistical excess of risk but with a positive trend for exposure levels are also considered as supportive evidence.
Data were also analysed for consistency in the results in different types of populations as positive associations in different populations strengthen the evidence that the effects are not due to confounders specific to one population (e.g. occupational co-exposures, socioeconomic factors). Each type of epidemiological study provides different information and consistency in the results from different epidemiological approaches (cohort or case-control studies) is also considered to strengthen the evidence. When relevant, the reasons for apparent inconsistencies were sought. The overall consistency of the available studies considering their respective strengths and limitations is also discussed.
In the overall conclusion, biological plausibility was also considered as an important element to evaluate the weight of evidence for causality.

Table 27 Synthesis of epidemiological data showing a positive association by site

Cancer site and type of studies	Statistically significant increase in risk supported by a statistical significant trend with at least one FA-exposure metrics	Statistically significant increase in risk with negative or not reported trend with FA-exposure metrics	Not statistically significant increase[a] in risk supported by a statistically significant trend with at least one FA-exposure metrics	Not statistically significant increase[a] in risk with negative or not reported trend with FA-exposure metrics	Overall appreciation based on: - significant evidence available from different type of populations (industrial workers *vs* professionals) - significant evidence available from different types of studies (cohorts *vs* case-control studies)
Sinonasal cancer					
Large industrial cohorts	-	-	-	NCI	Type of population[b] : - Type of studies [c]: +
Other industrial cohorts	-	Hansen 1995	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	Luce 1993 (adeno), Luce 2002 (adeno), Hayes 1986 (SCC)		Olsen 1984, Olsen 1986, Roush 1987, Luce 2000 (SCC)	-	

Oral cavity					
Large industrial cohorts	-	-	Coggon 2003	NIOSH	Type of population[b] : - Type of studies [c] : +
Other industrial cohorts	-	-	-	Marsh 2001 [d], Andjelkovic 1994, 1995 [d]	
Professional cohorts	-	Walrath 1984 [d], Hayes 1990 [d]	-	-	
Case-control studies	Wilson 2004[e]	-	-	Merletti 1991 [d], Gustavsson 1998	
Nasopharynx					
Large industrial cohorts	NCI	-	-	-	Type of population[b] : - Type of studies [c] : +
Other industrial cohorts	-	-	-	Hansen 1995	
Professional cohorts	-	-	-	Hayes 1990	
Case-control studies	West 1993, Vaughan 2000	-	Marsh 2007a, Vaughan 1986, Roush 1987 Hildesheim 2001	Olsen 1984	
Pharynx					
Large industrial cohorts	-	-	Coggon 2003	-	Type of population[b] : - Type of studies [c] : +
Other industrial cohorts	-	-	-	Marsh 2001 [d], Andjelkovic 1994, 1995 [d]	
Professional cohorts	-	Walrath 1984 [d], Hayes 1990 [d]	-	-	
Case-control studies	Laforest 2000	-	Marsh 2002	-	
Larynx					
Large industrial cohorts	-	-	Coggon 2003	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	Shangina 2006	-	-	Gustavsson 1998, Laforest 2000, Wortley 1992	
Lung					
Large industrial cohorts	Coggon 2003	-	-	-	Type of population[b] : - Type of studies [c] : +
Other industrial cohorts	-	Marsh 2001, Bertazzi 1989	-	Chiazze 1997, Andjelkovic 1994, 1995, Dell 1995	
Professional cohorts	-	-	-	-	
Case-control studies	De Stefani 2005	Coggon 1984, Youk 2001	Gerin 1989	Andjelkovic 1994, 1995	
Brain					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	Innos 2000, Chiazze 1997, Wesseling 2002	
Professional	Strout 1986	-	-	Hall 1991,	

cohorts				Walrath 1983, 1984, Levine 1984, Hayes 1990	
Case-control studies	-	-	-	Hauptmann 2009	
Stomach					
Large industrial cohorts	-	-	-	Coggon 2003	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	Stellman 1998	
Professional cohorts	-	-	-	-	
Case-control studies	-	-	-	-	
Rectum					
Large industrial cohorts	-	-	-	Coggon 2003	Type of population[b] : - Type of studies [c] : +
Other industrial cohorts	-	Innos 2000	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	Dumas 2000	-	-	-	
Pancreas					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	Dell 1995, Edling 1987	
Professional cohorts	-	-	-	-	
Case-control studies	Kernan 1999	-	-	-	
Prostate					
Large industrial cohorts	-	-	-	NIOSH	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	Walrath 1984	-	-	Hall 1991	
Case-control studies	-	-	-	-	
Breast					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	-	Hall 1991	
Case-control studies	-	-	-	-	
Colon					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	Walrath 1984	-	-	
Case-control	-	-	-	-	

studies					
Uveal melanoma					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	-	Holly 1996	-	-	
Oesophagus					
Large industrial cohorts	-	-	-	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	-	-	-	Gustavsson 1998	
Thyroïd					
Large industrial cohorts	-	-	-	NIOSH	Type of population [b]: - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	-	-	
Case-control studies	-	Wong 2005	-	-	
Leukaemia					
Large industrial cohorts	-	-	NCI (2003), NIOSH	-	Type of population[b] : - Type of studies [c] : -
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	-	Walrath 1984	Hall 1991, Walrath 1983, Levine 1984, Strout 1986	
Case-control studies	-	-	-	Linos 1990, Partanen 1993	
Myeloid leukaemia					
Large industrial cohorts	NCI (2003)	-	NIOSH	-	Type of population[b] : + Type of studies [c] : +
Other industrial cohorts	-	-	-	-	
Professional cohorts	-	Strout 1986	-	Walrath 1983, Walrath 1984, Hayes 1990	
Case-control studies	Hauptmann 2009	Linos 1990 (AML)	Blair 2001 (CML)	-	

[a] SMR, SIR or RR >1.10 but within the 95% confidence interval
[b] for type of population + is allocated if statistically significant association is observed with or without trend (two left columns) in both industrial and professional cohort studies; – is otherwise allocated.
[c] for type of studies + is allocated if statistically significant association is observed with or without trend (two leftcolumns) in both cohort and case-control studies; – is otherwise allocated.
[d] oral cavity and oropharynx or pharynx combined
[e] alcohol consumption not controlled

Cancers at the sites of contact

Sinonasal cancer:

A small non-significant elevated risk for nose and nasal cavity cancer was found in the NCI cohort but without a significant trend for any metrics (duration, average intensity, peak or cumulative exposure). The British (Coggon 2003) and the NIOSH cohorts failed to demonstrate any association. In other industrial cohorts, no case of nasal cancer was reported in several studies (Stellman 1998, Bertazzi 1989, Dell 1995, Edling 1987). A non statistical increase of cancer of the nose and sinuses was reported in the wood dust cohort (Innos 2000) but the increase of risk was higher in unexposed subjects than in subjects with a possible exposure to formaldehyde and the increase may have been caused by exposure to wood dust, a recognised etiologic factor for adenocarcinomas in the nasal cavity. In the Danish industrial cohort (Hansen 1995) an increase in the proportionate incidence of sinonasal cancers was observed and remains significant when subject with no wood dust exposure only were considered. In professional cohorts, no death from sinonasal cancer is reported. However, due to the small size of these professional cohorts, the expected number of case of sinonasal cancer is likely to be very low.

Several case-controls studies show an increased risk: the increase was not significant in Olsen *et al.* (1984) considering subjects unexposed to wood dust and in Olsen *et al. (*1986) for both adenocarcinomas and squamous cell carcinomas and it was significant in Hayes *et al.* (1986) for squamous cell carcinomas in subjects with no or low exposure to wood dust and in Luce 1993 for adenocarcinomas in the highest exposure category. A pooled analysis (Luce 2002) supports an elevated risk for adenocarcinomas with statistical significance the highest category of exposure and a positive trend with duration or intensity of exposure. Association was more important with adenocarcinomas than with squamous cell carcinomas whereas results for these two subtypes were similar in Olsen *et al.* (1986).
In meta-analyses, Partanen *et al.* (1993) found an increase in risk of borderline significance associated with higher exposure but it was not confirmed by Blair *et al.* (1990b) and Collins *et al.* (1997). All considered in their analysis both cohort and case-control studies. The latter study demonstrates a clear discrepancy of results between cohort (that overall indicate a risk deficit) and case-control studies (overall observing a significant increase of risk), in which a substantial heterogeneity of the results is observed (p=0.0001).

Evidence of a link between exposure to formaldehyde and induction of sinonasal cancer is provided in case-control studies. However, it is not observed in industrial or professional cohort as the positive association in the Danish cohort (Hensen 1995) is not reproduced in the largest industrial cohorts. In particular, the slight non-significant increase in risk observed in the NCI cohort is not supported by the existence of trends with exposure metrics. **There is some evidence from case-control studies and no or no significant evidence from available cohort studies. Data are considered to be insufficient to conclude on an association of formaldehyde exposure with sinonasal cancer.**

Oral cavity cancer:

No elevated risk was found in the NCI cohort whereas non-significant associations were observed in the NIOSH cohort and the British cohort (Coggon 2003) with an increasing risk with increasing level of exposure in the latter study. The other industrial cohort do not report increase of risk except a non-statistically significant increase in a iron foundry reported by Andjelkovich *et al.* (1995), in which buccal tumours and pharyngeal tumours were analysed together. In professional cohorts, buccal cancers were also pooled with pharyngeal cancers and results were largely inconsistent with some studies showing a decreased risk (Levine 1984, Strout 1986) while some others report a small non-significant increase (Walrath 1984, Hayes 1990).

Only three case-control studies are available and show a non-significant increase in cancer risk with no evidence of trend with duration in an analysis grouping oral cavity and oropharyngeal cancers (Merletti 1991) or no evidence of trend with intensity (Wilson 2004). A statistical increase in salivary gland cancers was observed in Wilson *et al.* (2004) in white men only but the analysis in this study was not controlled for alcohol consumption and link with formaldehyde exposure in these conditions is therefore uncertain.

Data from cohorts are inconsistent and no result from any reliable study attained statistical significance and data are not considered as sufficient to provide a causality relationship between formaldehyde and cancers of the oral cavity.

Nasopharyngeal cancer:

In the NCI cohort (Hauptmann 2004) which is the most important industrial cohort available in term of size and duration of follow-up, a twofold increase in the risk of nasopharyngeal cancer (statistically significant) was found. The increase is supported by positive trends with peak exposure (p trend < 0.001) and with cumulative exposure (p trend = 0.03). These results were confirmed when comparing the NPC mortality with local rates to take into account regional environmental factors (Marsh 2005). It however highlights that most NPC cases occured in the same plant (plant 1). Marsh *et al.* (2007b) also shows that risk estimates for NPC in the NCI cohort are unstable but this problem is linked with the rarity of NPC and the difficulty to provide evidence of association for small increases of rare cancers. In this study, a non-significant increase in the relative risk for NPC in the highest exposure category was however observed even after adjustment for plant group. Marsh *et al.* (2007a) also further investigate plant 1 of the NCI cohort in a nested case-control study, with the hypothesis that excess of NPC in plant 1 can be due to external employment in the ferrous and non-ferrous metal industries that entailed possible exposure to several suspected risk factor for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dust and fumes). A statistical association between NPC and working in silver smithing or other metal work has been identified. However, a non-statistically significant association between NPC and formaldehyde was still observed after adjustment for this factor as well as positive trends with duration of employment and with cumulative exposure but not with average intensity. Stratification by peak exposure, which was identified as the most significant metrics in Hauptman *et al.* (2004), was however not performed. Besides, a history of working in silver smithing or other metal work was not found in all NPC cases and cannot entirely explain the increase of NPC in the plant. Detailed information on types of jobs and exposures in metal work was also not available and it has not been possible to confirm that cases were actually exposed to any of the chemical agents that are suspected risk factors in this industry. These data were therefore not considered to be sufficient to explain the increase in NPC risk identified in the NCI cohort but raise a doubt on the existence of a cofounder in plant 1 of the NCI cohort. The analysis of the number of workers and level of exposure in the different plants included in the NCI cohort shows that plant 1 includes the largest number of subjects in the highest category of exposure to peaks (calculated on the basis of the data reported in Marsh *et al.* 2005): they are 1964 subjects exposed to the highest category of exposure to peaks in plant 1, 1864 in plant 10, 1233 in plant 4, 718 in plant

2 and less than 200 in other plants. Plant 1 is therefore the plant in which an excess of risk is the more likely to be identified.

Several other industrial cohorts investigate exposure to formaldehyde and found no evidence of an increased risk of pharyngeal cancer with no or very few cases reported. Given that nasopharyngeal tumours are rare (world incidence of 1.2 per 100 000 and mortality of 0.8 per 100 000 reported in GLOBOCAN 2008) and that these studies include a smaller number of subjects, the absence of an increased incidence is inconclusive. For example, the power to detect a twofold or greater increase in mortality from nasopharyngeal cancer was 13% in the NIOSH cohort and 44% in the British cohort (BfR 2006).

Small number of subjects is also a major weakness in the professional cohorts of pathologists and embalmers. In the two larger cohorts (around 4000 subjects), no nasopharyngeal cancers were observed in Hall *et al.* (1991) whereas a non-significant increase of tumours was reported in Hayes *et al.* (1990). Such cohort size that may have sufficient statistical power to detect an increase in common tumours but not for very rare tumours such as NPC

Several case-control studies investigate the association between exposure to formaldehyde and nasopharyngeal carcinoma (NPC). Although not statistically significant, formaldehyde exposure was associated with an increased risk of nasopharyngeal carcinoma, with supportive indications of higher risk with higher level of exposure (Vaughan 1986 and Roush 1987), duration of exposure (Vaughan 1986, West 1993 Hildesheim 2001 and Marsh 2007a), latency (Roush 1987 and West 1993) and cumulative exposure (Marsh 2007a). In West et al. (1993), the increase reached statistical significant with longer latency. Besides, Vaughan et al. (2000) reports an increase in risk with formaldehyde exposure unaffected by wood dust and that gained statistical significance when restricted to higher probabilities of exposure. In Olsen et al. (1984), an increase in risk was associated with formaldehyde exposure in women but not in men. In Amstrong *et al.* (2000), the risk was not increased after adjustment.

In the meta-analysis by Partanen *et al.* (1993), NPC risk was elevated with statistical significance in the substantial exposure category (exposure exceeding 5.5 ppm-year). NPC risk was also significantly elevated in Blair *et al.* (1990) and in Collins *et al.* (1997). Two recent meta-analyses (Bosetti 2008 and Bachand 2010) have highlighted the role of the NCI cohort and in particular of its plant 1 in the overall increase in risk. An overall increase in risk of borderline significance in pooled case-control studies was however observed in Collins *et al.* (1997) and in Bachand *et al.* (2010).

Significant evidence of an association between formaldehyde exposure and NPC is therefore provided from the most informative cohort study and from several case-control studies and meta-analyses. The NCI cohort is the most important in terms of cohort size and length of follow-up and is based on a detailed assessment of exposure. The increase in risk is supported by trends for several metrics of exposure. However, although the increase in risk may not be entirely explained by co-exposures investigated by Marsh *et al.* (2007a), the existence of a grouping of cases in NCI plant 1 can be explained by the largest number of subjects exposed to high peaks but also raise a doubt on potential cofounder.

It should also be noted that the majority of available studies are based on mortality and not on incidence. Because of its location, NPC may not cause symptoms at early stages, remains undetected and most NPC are diagnosed at an advanced stage with metastases typically in the cervical lymph nodes. Distant metastases may also occur in the bone, lung, mediastinum and more rarely, in the liver (Brennan 2006) with up to 80-90% of lymph node metastasis for the undifferentiated type (CHU-PS 2010). Due to the high rate of metastasis, it is expected in some cases that NPC may not be identified as the primary cause of deaths, resulting in an under-estimation of its incidence in cohorts. In addition, NPC is a rare tumour (Chang 2006), for which very large cohorts and statistical power are needed to be able to identify an excess of risk, Case-control studies are therefore considered as a critical source of information for NPC and predominantly indicate an increase of risk of NPC.

Overall, there is consistent evidence from the NCI cohort and from several case-control studies that formaldehyde may induce NPC. The existence of a grouping of cases in plant 1 of the NCI cohort raises a doubt on potential cofounder and lowers the level of evidence but it can also be explained by the largest number of subjects exposed to high peaks in this specific plant.

Pharyngeal cancers (other than nasopharyngeal or combined):

In industrial cohorts, a non-significant increased risk is observed in the British cohort (Coggon 2003) but not in the NIOSH cohort (no data on pharynx available in the NCI cohort). In professional cohorts and most other industrial cohorts, pharyngeal cancers were pooled with buccal cancers and results were largely inconsistent with some studies showing a decreased risk (Levine 1984, Strout 1986) while some others small non-significant increase (Walrath 1984, Hayes 1990). Four case-control studies are available and whereas Vaughan *et al. (*1983), Gustavsson *et al. (*1998) and Berrino *et al. (*2003) show no elevated risk, Laforest *et al. (*2000) observed a significant increase in cancer risk with evidence of trend with duration and cumulative dose.

Evidence of a link between exposure to formaldehyde and induction of pharyngeal cancer is provided in case-control studies and in particular in Laforest *et al* (2000). Data from cohorts are inconsistent and overall provide no clear evidence of an increased risk of pharyngeal cancer other than nasopharyngeal.

Laryngeal cancer:

A non significant elevated risk was reported in the British cohort study (Coggon 2003) only in the high exposure category. No elevated risk was observed in other industrial cohorts and no results for laryngeal cancers were reported in professional cohorts. Non-significant increases in the case-control studies by Wortley *et al.* (1992) at high dose only and in Gustavsson *et al.* (1998). The increase was however statistically significant in the highest category of cumulative exposure in Shangina *et al.* (2006).

Data from cohort studies therefore provide no evidence of an increased risk of laryngeal cancer to support the slight increase identified in some case-control studies.

Lung cancer:

In the British industrial cohort (Coggon 2003), an elevated risk of lung cancer was associated with higher intensity but not with longer duration of exposure. Results in the two other large cohort studies do not confirm this result. In other industrial cohorts, positive results are reported in cohorts co-exposed to MMVF (Marsh 2001, Chiazze 1997), asbestos (Dell 1995) or silica (Adjelkovic 1994). No increased risk was detected in any professional cohorts. In case-control studies, Andjelkovich *et al.* (1994) showed a non-significant increased risk. The increase reached statistical significance in two case-control studies (Coggon 1984, Youk 2001) but with negative trends with exposure. An excess of risk in workers exposed to formaldehyde with a significant trend with duration of exposure was observed in a third case-control study that investigate specifically lung adenocarcinomas (De Stephani 2005). In meta-analyses, whereas Collins *et al.* (1997) found no increased risk, Partanen *et al.* (1993) found a weak positive effect

of borderline significance but risk was not increased with higher exposure category. Finally, a positive association was found in industrial workers and a negative in professional workers (Blair 1990).
Overall, the inconsistency of the results in the large industrial cohorts, the discrepancy between results in industrial and professional workers and the potential cofounders in small industrial cohorts does not allow to identify an association between formaldehyde exposure and lung cancer.

Cancer at distant sites

Lymphohaematopoietic malignancies:

An excess of lymphohaematopoietic cancers is reported most specifically for leukaemia. A non-statistically significant increase was reported in two large industrial cohorts with support of positive trends for peak and average intensity (NCI cohort in Hauptmann 2003) and for duration and time since first exposure (NIOSH cohort). Non-statistically significant increases in risk were reported in several professional cohorts that were supported with trend for duration in Walrath *et al.* (1984) but not in Strout *et al.* (1986) as well as in two case-control studies.

Statistical significance was however attained in several studies investigating more specifically a potential increase in risk for myeloid leukaemia. In the NCI cohort (Hauptmann 2003), excess in relative risks for myeloid leukaemia were statistically significant in the categories of highest peak and average intensity exposure, with statistically significant trends for these two metrics but not for duration or cumulative exposure. A re-analysis of the NCI cohort (Marsh 2004) found no significant excess of risk for external comparison (SMR) but confirmed a statistically significant excess of risk in the highest peak exposure categories based on internal comparison (RR). These high RR were explained by very low incidence of ML in unexposed and control groups (low exposure group). Risk estimates however declined in the more recent update of the NCI cohort (Beane-Freeman 2009). Considering a relatively short period of latency for myeloid leukaemia, the reduction of association after the 1990s could however reflect a reduction in levels of exposure with time. A statistical excess of risk was also observed in a professional cohort (Strout 1986) and in two case-control studies: Linos *et al.* (1990) was focused on acute myeloid leukaemia more specifically. Hauptmann *et al.* (2009) also investigate trends with different metrics of exposure and found positive association with duration of practice and peak exposure.

Finally, results of two meta-analyses show significant increases in leukaemia only in professionals (Blair 1990b, Bosetti 2008). The study by Collins *et al* (2004) confirms the discrepancy in the results from different high exposure occupations, with an absence of increased risk in industrial workers. A recent meta-analysis however found overall significant results for leukaemia and myeloid leukaemia but this study focused on highest exposure group from each study considered in the meta-analysis (Zhang 2009). Consideration of higher levels of exposure is expected to generate a greater statistical power to detect a relationship if a true effect exists. The study by Zhang (2009) was updated in Schwilk *et al.* (2010) using the same methodology and including the latest updates and epidemiology studies (in particular Hauptmann 2009 nd Beane-Freeman 2009). An excess of risk of 2.47 was found for myeloid leukaemia. Based on a similar set of study but taking into account RR estimates for all levels of exposure, Bachand *et al.* (2010) did not identify a statistical increase in RR estimates.

Overall, some positive observations have emerged in industrial populations but meta-analyses generally show a discrepancy in the results between industrial and professional populations in which several studies indicate an increased risk of leukaemia and especially myeloid leukaemia. Therefore, it is considered that available data does not provide causal evidence for formaldehyde as the aetiological factor as a bias specific to professionals cannot be ruled out.

Brain cancers:

Brain cancer risk was similar to expected in the NIOSH cohort and lower than expected in the NCI and British cohorts. A non-significant increase in risk was observed in two small industrial cohorts but with no trend with exposure (Innos 2000) and higher risk in unexposed subjects (Chiazze 1997). Several non-significant (Hall 1191, Walrath 1983, Walrath 1984, Levine 1984 and Hayes 1990) and significant (Strout 1986) increases in risk were consistently reported in professional cohorts. The discrepancy between industrial and professional cohorts is highlighted by meta-analyses showing significant increases in professional cohort but not in industrial workers (Blair 1990, Bosetti 2008). The only case-control study investigating this cancer type reports a non statistical increase (Hauptmann 2009). However, it was not supported by trends with duration of practice, peak, cumulative or average intensity exposures and was considered not conclusive for brain cancer. **In absence of other evidence from industrial cohort or case-control studies, the effect observed in professionals is more likely to be due to confounding factors.**

Other cancers:

Isolated results across studies suggest an elevated risk of cancers at other sites such as:

- Stomach: non-significant increase in risk in the Bristish cohort (Coggon 2003) and in another industrial cohort (Stellman 1998), more likely to be due to confounding factors as it was not confirmed in the other large industrial cohorts or in professionals.
- Rectum: increase in risk of borderline significance in a small industrial cohort (Innos 2000) and significant increase in the only case-control study investigating this cancer type with positive trends with concentration and duration of exposure (Dumas 2000). In this study, many substances showed associations with rectal cancer and it was not possible to clearly assign the observed effect to formaldehyde or to another substance independently. Besides, the absence of increases in risk in large industrial cohorts and in professionals does not support an association of formaldehyde with rectum cancer.
- Pancreas: non-significant increase in risk in two small industrial cohorts (Dell 1995 and Edling 1987) and significant increase in the only case-control study investigating this cancer type with trends with probability but not with intensity of exposure (Kernan 1999). However, the absence of increases in risk in large industrial cohorts and in professionals does not support an association of formaldehyde with pancreas cancer.
- Prostate: non-significant increase in risk in one professional cohort (Hall 1991) and significant increase in another professional cohort with a trend with duration of exposure (Walrath 1984). However, the absence of increases in risk in industrial cohorts does not support an association of formaldehyde with prostate cancer. No relevant case-control study is available on prostate cancer.
- Breast: isolated non-significant increase in risk in one professional cohort (Hall 1991)
- Colon: isolated significant increase in risk in one professional cohort (Walrath 1984)

- Uveal melanoma: isolated significant increase in risk in the only case-control study investigating this cancer type (Holly 1996)
- Oesophagus: isolated non-significant increase in risk in the only case-control study investigating this cancer type (Gustavsson 1998) not supported by trend for cumulative or duration of exposure.
- Thyroid: isolated significant increase in risk in the only case-control study investigating this cancer type (Wong 2005).

However, these results were highly inconsistent for stomach, brain, colon, pancreas and prostate with excess of cancers limited to either industrial workers or professionals and not identified in the largest industrial cohorts. Other results were isolated and it cannot be excluded that they are due to confounding factors.

4.10.5 Comparison with criteria

For experimental data, the CLP criteria for classification establish different levels of evidence:

— *"**sufficient evidence of carcinogenicity**: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;*

— ***limited evidence of carcinogenicity**: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs."*

Experimental data clearly provide evidence of a carcinogenic effect at the site of contact in rats by inhalation. Although this finding is restricted to a single species (rat), consistent results were obtained from several independent studies and in both females and males. Tumours consists in both benign and malignant tumours but were induced at a single site (nasal cavity). Data investigating the mode of action support the existence of a threshold type mode of action for its carcinogenic properties based on the cytotoxic effect of formaldehyde. Genotoxicity is also expected to play a role above this threshold.

Overall the level of experimental evidence is judged as sufficient evidence in agreement with induction of tumours (b) [in] two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

For epidemiological data, the CLP criteria for classification establish different levels of evidence:

- *"**sufficient evidence of carcinogenicity**: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;*
- ***limited evidence of carcinogenicity**: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."*

At the site of contact, positive associations between exposure to formaldehyde and cancer were identified from both cohort studies and case-control studies for cancers of the sinonasal cavity, oral cavity, nasopharynx, pharynx and lung. Results were statistically significant and supported by trends with exposure in both types of studies for nasopharynx, which provide a high level of evidence of an association. However, the existence of a grouping of cases in plant 1 of the NCI cohort raises a doubt on potential cofounder and lowers the level of evidence but the grouping of cases can also be explained by the largest number of subjects exposed to high peaks in this specific plant. .

Several factors support the existence of a carcinogenic potential of formaldehyde at the site of contact:

- Induction of tumours in the nasal cavity in rats with a proposed mode of action based on chronic irritation of the respiratory tract and local genotoxicity at doses inducing cytotoxicity and increased proliferation
- Indication of local genotoxicity in exposed humans as evidenced by increases in micronuclei frequency in buccal and nasal mucosa cells in several studies
- Human sensitivity to FA-induced irritation, with irritation of the eye and of the nose/throat consistently reported after exposure to formaldehyde (IARC 2006).

No species-specific mechanism is evident and human data denote human sensitivity to FA effects (genotoxicity and irritation). The mode of action of carcinogenicity in the rat nasal cavity is therefore considered relevant to humans, as reviewed in the context of the IPCS framework (McGregor 2007).

It is noted that the site of local tumours in rats (nasal cavity) and in humans (nasopharynx) differs. Humans, unlike rats, are oronasal breathers and dosimetry in the different parts of the respiratory tract is expected to be different. In rats, lesions and DPX formation were mainly observed in the lateral meatus of the nasal cavity. In rhesus monkeys, DPX are also formed in proximal portions of the lower respiratory tract in rhesus monkeys (Casanova 1991). Modeling of FA dosimetry in the respiratory tract indicates that when the switch to oronasal breathing occurs, cells in the upper segments of the lower respiratory tract receive a considerably higher flux of formaldehyde from oral intake (Conolly 2004). Difference in the site of tumours in the respiratory tract is therefore not in contradiction with the relevance of the rat data for humans.

The induction of nasopharyngeal carcinomas in human exposed to formaldehyde is therefore strongly plausible.

The biological plausibility of the induction of nasopharyngeal carcinomas in humans exposed to formaldehyde highly supports the consistent epidemiological evidence obtained from the NCI cohort and from several case-control studies. It is considered that the doubt of a potential confounder is raised by the grouping of cases in the plant 1 of the NCI cohort. But considering the overall database and more specifically the fact that the grouping of cases in plant 1 can also be explained by the largest number of subjects exposed to high peaks in this specific plant, correlation of NPC with the level of peak exposure to formaldehyde, the evidence provided by case-control studies and the biological plausibility, the doubt that the observed induction of NPC may be due to chance, bias or confounding can be ruled out *with reasonable confidence.*

Altogether, the data support a causal relationship between formaldehyde exposure and induction of NPC and corresponds to a sufficient evidence of carcinogenicity in humans.

<u>At distant site,</u> excess of risk are reported for myeloid leukaemia. Some positive observations have emerged in industrial populations but meta-analysis show a discrepancy in the results between industrial and professional populations in which several studies indicate an increased risk of leukaemia and especially myeloid leukaemia. Therefore, it is considered that available data does not provide causal evidence for formaldehyde as the aetiological factor as a bias specific to professionals cannot be ruled out.

Besides, inhalation of formaldehyde doesn’t modify formaldehyde blood levels in rats, monkeys and humans and due to its high reactivity, its rapid metabolism and detoxification formaldehyde is not expected to reach distant site and the biological plausibility for induction of leukaemia is therefore weak (Heck 2004). Finally, no convincing evidence for induction of tumours in the lympho-haematopoietic system is identified in experimental animals whereas haemopathies are observed in rodents with known leukemogens. This potential mode of action was discussed in several reviews funded by the FA industry (Casanova 2004, Golden 2006, Pyatt 2008, Rhomberg 2011) or in a recent ECETOC/ILSI/HESI workshop (Carmichael 2011) that concluded that no convincing mechanism has been indentified si far.

However, several observations have emerged recently and tend to indicate that formaldehyde may have systemic effects, in particular on the lympho-haematopoietic system:

- Evidence for induction of genotoxicity (micronuclei) in peripheral lymphocytes in humans. Inconsistent results are however reported for induction of SCE and chromosomal aberrations. Besides, negative results on bone marrow and blood cells were obtained in rats by inhalation under controlled conditions.

- Report in a recent study (Zhang 2010) of an increase in the frequency in the myeloid progenitor cells from peripheral blood of exposed workers of loss of chromosome 7 (p=0.0039) and of trisomy of chromosome 8 (p=0.040), which are among the most frequent cytogenetic changes observed in myeloid leukaemia. Cytogenetic anomalies were however analysed on a very limited number of cells (150/subjects) and subjects (10 exposed and 12 controls) and it cannot be excluded that the observed effect may reflect individual heterogeneity considering that these anomalies are also found in non-exposed subjects. Besides, the meaning of these cytogenetic anomalies is not known in terms of molecular oncogenesis. They are not known to be sufficient to induce the apparition of a leukemic phenotype and are also present in control subjects at a substantial frequency

It is regrettable that additional cytogenetic anomalies characteristic of myeloid leukaemia and which have a clear biological significance as they re-arrange genes involved in proliferation or differentiation (e.g. translocations t(8;21), t(9;22) or t(15;17)) have not been investigated. Due to the very small number of subjects the study therefore need to be replicated.

- Recent formulation of hypothesis for potential modes of action (Zhang 2009):
  - transport in the blood in the hydrated form methanediol and damage of stem cells in the bone marrow.

  Considering the chemistry of formaldehyde in solution, the equilibrium between formaldehyde and methanediol is largely in favour of methanediol under physiological conditions (37°C and pH 5-7) but a proportion of 1% of the substance is also present as formaldehyde. As formaldehyde is highly reactive and is likely to quickly disappear by linking to macromolecules where it is produced, spontaneous release of formaldehyde from methanediol may take place to maintain the equilibrium between methanediol and formaldehyde. A small but continuous production of formaldehyde can therefore take place at distant sites where methanediol is present. However, the level of methanediol in blood (reported as formaldehyde in the publications by misuse of language but GC-MS actually measures methanediol and formaldehyde together) further to inhalation exposure to formaldehyde did not raise (Heck 2004). A mathematical model also predicted that the increase of the formaldehyde concentration (reflecting both free and hydrated forms) in blood further to inhalation exposure is insignificant compared to endogenous levels of formaldehyde (Franks 2005). Besides, the radioactivity incorporated in the blood and bone marrow further to inhalation of [^{14}C] FA was due to metabolic incorporation and not to covalent binding (Casanova-Schmitz 1984). Lu et al (2010, 2011) recently showed in rats that N2-hydroxymethyl-dG adducts and dG-dG crosslinks from exogenous origin were detected further to inhalation of radiolabelled formaldehyde in nasal respiratory epithelium but not in bone marrow, spleen, lung, liver, thymus tissues or blood in rats. N2-hydroxymethyl-dG adducts was also not detected in the bone marrow of monkeys up to 6 ppm. N2-hydroxymethyl-dG adducts was found to be a suitable biomarker for formaldehyde exposure in preliminary cell culture experiments.

  Besides, a recent studies (Neuss 2008 and Neuss 2010b) has shown that formaldehyde is not released from exposed cells and DPX and SCE are observed only in cells in direct contact with formaldehyde.
  The hypothesis that formaldehyde may be transported to the bone marrow by damaged cells or as active forms is therefore considered unlikely.

  - damage to stem cells circulating in the blood at the site of contact and re-incorporation of damaged stem cells in the bone marrow.

  Hematopoietic stem cells present in blood have however a short half life in circulation estimated around 1-2 hours (Papayannopoulou 2008) and they are 100 less numerous in blood than in bone marrow where they represent only 1-3% of normal cells. Besides, they have a very intermittent and brief exposure considering the number of passage of each stem cell in the nasal tracts and the short duration of transit of cells in this area. It would therefore be expected that a similar mode of actions would occur with other factors such as UV radiations

that may reach blood cells by cutaneous exposure. Such effects has however not been identified.
The possibility for haematopoietic stem cells to go from the bone marrow to blood and inversely is known (homing). However, it has never been observed in the case of damaged circulating progenitor cells giving rise to leukaemia either with formaldehyde or other leukemogen factors.

- damage to primitive pluripotent stem cells present in the oral and nasal mucosa and re-incorporation of damaged stem cells in the bone marrow.

All flat bones are haematopoietic in adults and haematopoietic stem cells are expected to be present in the ethmoid and nasal bones. But the penetration of formaldehyde to the marrow of these bones seems not compatible with its reactivity. Murrell *et al.* (2005) has demonstrated in rats that cells able to differentiate into haematopoietic stem cells were present in the nasal mucosa as they repopulate the bone marrow of irradiated hosts. Additional experiments indicate that this effect was not attributable to the presence of hematopoietic stem cells in the olfactory mucosa sample but to other stem-like cells. The presence of such stem cells able to differentiate *in vitro* and *in vivo* into multiple cell types was also found in the olfactory mucosa of mice and humans but they were not shown to differentiate into haematopoietic cells.
The presence of haematopoietic stem cells in the nasal mucosa has been demonstrated (Sergejeva 2005). But a genotoxic and leukemogenic effect of formaldehyde on these cells would induce an increase in the frequency of chloromas (accumulation of leukemic cells in tissues) in the nasal mucosa of exposed subjects but this has not been reported.
This hypothesis is also not supported by the fact that many nasal carcinogens are not identified as leukemogens. It is the case of chromium, nickel or arsenic compounds. Only sulphur mustard is proved to be a nasal carcinogen an induced pancytopenia in heavily exposed subjects (Goldstein 2010).
As in the previous hypothesis, the possibility for damaged circulating progenitor cells to go back to the bone marrow and to give rise to leukaemia is also not demonstrated.
Besides, a recent study (Kuper 2011) has investigated in animals the effect of FA on nasal lymphoid tissue further to inhalation. The 28-day study revealed hyperplasia of the lymphoepithelium in the NALT at 15 ppm in rats but no significant effect on the NALT lymphoid tissue or in the cervical lymph nodes (decreased NALT activity in some animals but no significant effect compared to controls). No effects were detected at similar doses in mice that are less sensitive than rats to FA damage in the nasal mucosa. This tends to show that FA does no induce a proliferative effect in the nasal lymphoid tissues that could participate in haematological malignancies..

- Indications that formaldehyde may produce toxicity to white blood cells in humans (Zhang 2010). A decrease in white blood cell counts was observed in exposed workers but the values remains in the normal range. A decrease in colony formation from exposed human progenitor blood cells was also observed but the effect was not statistically significant and the meaning of this finding in terms of toxicity or inhibition is not clear. Indeed, a dose-related decrease in the number colony formed by progenitor cells was observed *in vitro* but this is not surprising considering the cytotoxic effect of formaldehyde. Besides, pancytopenic effects are not found in long-term studies in rodents to the maximally tolerated doses (Goldstein 2010). No effect on blood count related to FA exposure was detected in Kuo *et al.* (1997) but exposure in this study was very low. A higher sensitivity of humans may be hypothesised to explain this difference but it has not been further explored and demonstrated by any element up to now.

These elements are therefore considered as preliminary evidence. Besides, the study by Zhang et al (2010) tends to show an effect on blood cells and progenitor cells in peripheral blood but it provides no evidence of a direct effect in the bone marrow.

Altogether, in absence of convincing evidence for a biologically plausible mechanism and considering the discrepancy of results in epidemiological studies, a causal relationship between formaldehyde exposure and induction of myeloid leukaemia cannot be concluded.

Overall, CLP criteria for classification states:

"The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:

— *[1A:] human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or*
— *[1B:] animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).*

In addition, on a case-by-case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals."

A category Carc 1A is therefore warranted for formaldehyde for carcinogenicity at the site of contact and more specifically induction of NPC. Sufficient evidence in humans is concluded based on consistent evidence from the NCI cohort and from several case-control studies supported by animal data and biological plausibility.

4.10.6 Conclusions on classification and labelling

A classification Carc 1A – H350 is warranted (carc . cat. 1 ; R45 according to Directive 67/548/EEC).

The proposed carcinogenic classification is entirely based on data obtained by the inhalation route either in humans or in experimental animals. The route of exposure can be specified in the hazard statement "if it is conclusively proven that no other routes of exposure cause the hazard". Reliable studies are available in experimental animals by the oral route but not by dermal route. In humans, it is expected that due to formaldehyde uses and physical properties only data resulting from respiratory exposure will be obtained. However, the present database does not allow proving that formaldehyde does not have a carcinogenic effect by dermal route and the route of exposure cannot be specified in the hazard statement.

The relevance of setting specific concentration limits was assessed based on the recommended guidance (EC 1999). It is based on the evaluation of potency, which is defined as “the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration”.

The proposed classification Carc 1A is based on nasopharyngeal cancers in humans. Evaluation of potency in humans is however difficult as specified in the guidance. The lack of precise exposure measurement do not allow establishing a reliable dose-response curve and EC guidelines recommend to assess the potency calculation on the dose that produces a tumour incidence of 25% (T25) in experimental studies. However, it also mention in section 2.5 that determination of T25 value is not appropriate in the case of a non-systemic contact carcinogen, as in the case of formaldehyde. A SCL cannot therefore be derived.

4.11 Toxicity for reproduction

Not evaluated in this dossier.

4.12 Other effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

The information included in this report is based on a bibliographic search perfomed in April 2010 and supplemented by articles identified by a search alert up to the date of submission of the report.

Registration dossiers available in May 2011 were rewieved. Information in part 7.6 (Genetic toxicity), 7.7 (Carcinogenicity) and 7.10 (Exposure related observations in humans) that was not already present in the CLH report (version 1) was included in the revised version when relevant in the discussion of carcinogenic or mutagenic effects, performed through a relevant route of exposure, and available in english language.

A discussion with the formaldehyde industry was organised in the preparation of this dossier in the form of a meeting with Formacare on July 18th 2011. Their position on carcinogenic classification of formaldehyde is included in the IUCLID 5 dossier (Formacare position paper).

Formaldehyde has been studied for a long time and reviews of the toxicological properties of formaldehyde were performed by several international or national organisation. The main recent reviews (issued after 2005) that discuss mutagenicity and/or carcinogenicity of formaldehyde are:

- Carcinogenicity of formaldehyde was evaluated in 2006 by the BfR that concluded that there is sufficient evidence to assume a causal relationship between formaldehyde exposure and induction of nasopharyngeal cancer in humans (BfR 2006).
- IARC evaluated carcinogenicity of formaldehyde in a monograph published in 2006 (IARC 2006). Formaldehyde IARC classification has been revised in 2009 (Baan 2010). Although the resulting monograph is not published yet, the IARC Working Group unanimously reaffirmed the classification of formaldehyde in Group 1, based on sufficient evidence in humans of nasopharyngeal cancer. The Working Group concluded that, overall, there is sufficient evidence for leukaemia, particularly myeloid leukaemia.Formaldehyde is under discussion at NTP to revise its listing status under the 12th Report of Carcinogen (ROC). A background document on carcinogenicity of formaldehyde has been published in 2010 (NTP 2010a). A DRAFT recommendation to list formaldehyde as a *known to be a human carcinogen* based on evidence of causality for nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia in June 2010 (NTP 2010b) but is still under discussion.
- The US EPA has published in June 2010 a DRAFT toxicological review of inhalation toxicity of formaldehyde (EPA 2010) concluding that “Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, myeloid leukemia and lymphohematopoietic cancers as a group.” The National Research Council (NRC) reviewed this draft assessment and concluded (NRC 2011) that on respiratory tract cancers, “the committee agrees that there is sufficient

> evidence […] of a causal association between formaldehyde and cancers of the nose, nasal cavity, and nasopharnyx. It disagrees that the evidence regarding other sites in the respiratory tract is sufficient. […] Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality."

These reviews are attached for information in the IUCLID dossier.

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