SCOEL/REC/125
Formaldehyde

Recommendation from the
Scientific Committee on Occupational Exposure Limits

Scientific Committee
on Occupational Exposure Limits

H.M. Bolt, G. Johanson, G. D. Nielsen, D. Papameletiou, C. L. Klein
Adopted 30 June 2016

SCOEL/REC/125
Formaldehyde

Recommendation from the
Scientific Committee on Occupational Exposure Limits

Scientific Committee on Occupational Exposure Limits
2016

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

Contact: Dr. Christoph Klein

E-mail: *EMPL-SCOEL@ec.europa.eu*
Christoph.Klein@*ec.europa.eu*

European Commission
B-1049 Brussels

Scientific Committee on Occupational Exposure Limits

2016

ED_014350_00001020-00004

Europe Direct is a service to help you find answers to your questions about the European Union.

Freephone number (*)**:**

00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

LEGAL NOTICE

This document has been prepared for the European Commission however it reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

More information on the European Union is available on the Internet (http://www.europa.eu).

Luxembourg: Publications Office of the European Union, 2014

ISBN: 978-92-79-64151-0
doi: 10.2767/399843

© European Union, 2015
Reproduction is authorised provided the source is acknowledged.

Table of Contents

TABLE OF CONTENTS 5
RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR FORMALDEHYDE 7
RECOMMENDATION EXECUTIVE SUMMARY 8
RECOMMENDATION REPORT 11
1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES 11
2. EU HARMONISED CLASSIFICATION AND LABELLING 12
3. CHEMICAL AGENT AND SCOPE OF LEGISLATION 12
4. EXISTING OCCUPATIONAL EXPOSURE LIMITS 13
5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE 14
5.1. Occurrence and use 14
5.2. Production and use information 15
5.3. Occupational Exposure 15
5.4. Routes of Exposure and uptake 15
6. MONITORING EXPOSURE 16
7. HEALTH EFFECTS 17
7.1. Toxicokinetics, Absorption, Distribution, Metabolism, Excretion (ADME) 18
7.1.1. Human data 19
7.1.2. Animal data 20
7.1.3. In vitro data 20
7.1.4. Biological monitoring 20
7.2. Acute toxicity 21
7.2.1. Human data 21
7.2.2. Animal data 21
7.3. Specific Target Organ Toxicity/Repeated Exposure 21
7.3.1. Human data 21
7.3.2. Animal data 21
7.3.3. In vitro data 22
7.4. Irritancy and corrosivity 22
7.4.1. Human data 22
7.4.2. Animal data 25
7.4.3. In vitro data 25
7.5. Sensitisation 25
7.5.1. Human data 25
7.5.2. Animal data 25
7.6. Genotoxicity 26
7.6.1. Human data 26
7.6.2. Animal data 31
7.6.3. In vitro 33
7.7. Carcinogenicity 34
7.7.1. Human data 34
7.7.2. Animal data 42
7.8. Reproductive toxicity 44
7.9. Mode of action and adverse outcome pathway considerations 44

ED_014350_00001020-00006

Experimental findings: 44
Epidemiological findings: 45
Integrating toxicokinetics and mode of action 46
7.10. Lack of specific scientific information 49
7.11 Recommendation, health considerations 50
8. GROUPS AT EXTRA RISK 53
9. REFERENCES 54

ED_014350_00001020-00007

Recommendation from the Scientific Committee on Occupational Exposure Limits for Formaldehyde

8-hour TWA:	0.3 ppm (0.369 mg/m^3)
STEL:	0.6 ppm (0.738 mg/m^3)
BLV:	-
Additional categorisation:	SCOEL carcinogen group C (genotoxic carcinogen with a mode-of action based threshold)
Notation:	Sensitisation (Dermal)

The present Recommendation was adopted by SCOEL on 30 June 2016.

This evaluation is based on a previous evaluation by SCOEL (SCOEL/SUM/125; March 2008), the data compilations in the CLH report (ECHA, 2011), the reviews of Nielsen and Wolkoff (2010), Wolkoff and Nielsen (2010), IARC (2012), Checkoway et al. (2012), Nielsen et al. (2013), Bolt and Morfeld (2013), DFG (2014), the conclusions of the Risk Assessment Committee (RAC, ECHA, 2012) of the European Chemicals Agency (ECHA) and a further literature search in 2015.

In the present Recommendation, "FA" is used as an abbreviation for formaldehyde throughout.

ED_014350_00001020-00008

Recommendation Executive Summary

When reviewing the scientific data available for formaldehyde (FA), SCOEL recognised that FA is a very well investigated substance, for which a high number of reliable high-quality studies relevant for the occupational situation are available. This includes a variety of epidemiological studies on exposed workers, studies on human volunteers for sensory irritation and a broad database on experimental animal studies.

SCOEL has assessed all available information. FA has a potential to cause adverse health effects and is therefore a hazardous chemical agent. FA also is a genotoxic carcinogen, for which a mode-of-action based limit value can be derived. For FA the available information is adequate for deriving a health-based OEL (8-hour TWA and STEL).

Analytical measurement systems exist to determine the recommended levels of formaldehyde with an appropriate level of precision and accuracy.

Due to the high water solubility and the high reactivity of FA, it shows intrinsic hazardous properties predominantly with respect to local effects. In addition, directly induced systemic effects of inhalation at concentrations relevant for the workplace are considered unlikely. The following key effects were considered as being relevant for the protection of workers and in particular the OEL derivation:

(a) the potential of the substance to produce respiratory irritation and chemosensory effects, both in humans and animals, and

(b) the local carcinogenicity in studies with experimental animals exposed by inhalation.

Ad (a): Sensory irritation has been investigated in experimental animals, in exposed workers, and most importantly also under controlled exposures in volunteers.

Ad (b): Tumour induction of the upper respiratory tract has been studied in experimental animals including mechanistic investigations on events that will trigger carcinogenesis, like DNA-protein crosslinks (DPX), DNA-adducts and sustained cytotoxicity leading to cell proliferation. In addition, several high quality epidemiological studies are available on exposed workers. A review by RAC (ECHA 2012) concluded that these data would not provide sufficient evidence to classify FA as a human carcinogen but a classification as Cat. 1B carcinogen (H350 "May cause cancer"; based on CLP criteria) would be appropriate.

Mechanistic studies have provided strong evidence that tumour induction in the nasal mucosa of rats and mice is the result of chronic proliferative processes caused by the cytotoxic effects of the substance in combination with DNA alterations by endogenous and exogenous FA. The dose-response relationships for all parameters investigated, such as damage to the nasal epithelium, cell proliferation, tumour incidence, the formation of DPX and DNA-adducts, is very flat for low level exposures and becomes much steeper at higher concentrations. For these endpoints no-effect concentrations were demonstrated with the exception of the formation of DPX and DNA-adducts. However, at the lowest concentrations investigated so far (0.7 ppm), adducts caused by the endogenous, physiological FA by far exceeded the amounts caused by exogenous FA. The background incidence of nasal tumours in rodents and of nasopharyngeal tumours in humans is very low in spite of the appreciable amount of endogenous DNA adducts. One of the reasons may be the low physiological proliferation rate of the respiratory epithelium, and as long as this is not increased (which requires exposure to concentrations of more than 2 ppm), the probability of tumour formation also is low. At prolonged exposure at 2 ppm in rats, the half-life of the most sensitive biomarker of DNA-adducts, N^2-hydroxymenthy-dG, was 7 days. At 2 days of exposure in monkeys, the biomarker was estimated to be by a factor of 5-11 lower for the exogenous adduct than that of the endogenous adduct in the nasal

ED_014350_00001020-00009

epithelium. Comparing short term exposures, the relationship of exogenous/endogenous DNA–adducts was by a factor of about 5-fold lower for monkeys than for rats, suggesting monkeys being a less sensitive species than rats. Taking into consideration the strong non-linearity of the dose response curve after a single exposure at lower exposure concentrations, the ratio between exogenous/endogenous adducts will at low exposures be dominated by the endogenous adducts, but the ration will increase disproportionately with increasing FA concentrations. Also in the low dose range, cell proliferation is not increased. It has therefore been considered that the genotoxicity of FA plays no or at most a minor role in a potential carcinogenic effect at this exposure-range.

Therefore SCOEL considers FA as a group C carcinogen (genotoxic carcinogens for which a limit value derived from mode-of-action based threshold is supported) (SCOEL, 2008).

Experimental studies support that the local carcinogenesis at the portal-of-entry is pivotal. In the sensitive rat species, the apparent LOAEC was 6 ppm, and the apparent NOAEC was 2 ppm for nasal cancer. Experimentally, the histopathological NOAEC for nasal effects of FA in rats and monkeys is 1 ppm and the NOAEC for regenerative cell replication 2 ppm. At these NOAECs, the FA-DNA adducts were less in monkeys than in rats as was the relationship of exogenous/endogenous DNA adducts, which is in line with the assumption that humans should be a less sensitive species. The new studies confirm that local FA-DNA adducts show a highly non-linear relationship with external FA exposures. At ≤ 2 ppm FA, the FA DNA-adducts induced by external exposures comprise a minor portion of the total FA-DNA adducts, which were driven mainly by internal (naturally generated) FA. This is supported by considerations on toxicokinetics, concluding that the intracellular FA concentration increases only slightly, and the intracellular glutathione concentration decreases only slightly in this range and that the homeostasis within the epithelial cells would not be affected. Therefore, the apparent NOAEC of 1 ppm can be considered a mode-of-action based NOAEC for carcinogenic effects at the portal-of-entry.

Ad (a): Preventing histopathological effects, like irritation, inflammation and regenerative cell replication caused by cytotoxic irritation, will also prevent nasal cancer as at such low exposure concentrations (< 1 ppm) the total intracellular FA concentration is dominated by the internal (natural) FA. This experimentally derived paradigm, namely the avoidance of cell proliferation in the upper respiratory tract being critical to prevent local carcinogenicity, also holds valid for humans. Ideally the lower sensitivity against cytotoxic irritation of humans as compared to rats should be taken into consideration. While cytotoxic irritation cannot be investigated in humans, mainly for ethical reasons, there is a broad database available for sensory irritation from volunteer studies under controlled exposure conditions. By derivation of limit values for sensory irritation of eye and upper respiratory tract in humans also the critical effects of irritation-induced local cell proliferation and subsequent possible carcinogenesis shall be covered (Brüning et al 2014).

In this respect, numerous studies, comprising in total more than 400 volunteers, have addressed human sensory irritation effects of FA. The Paustenbach et al (1997) review [and two similar reviews of Bender (2002) and Arts et al. (2006)], concluded that sensory irritation would seldom be observed at 0.5 ppm FA and extrapolated these results to suggest that a limit of 0.3 ppm would prevent sensory irritation in nearly all occupational exposed individuals. Two recent chamber studies (Lang et al. 2008; Mueller at al. 2013) found no pure sensory irritation, as measured by objective parameters, in the concentration range from 0.5 to 0.7 ppm at a constant exposure to FA during a 4-hour period. Both studies applied slightly different concentration regimes. Exposures with 4 superimposed peaks being most relevant for derivation of an OEL with STEL were 0.3 ppm + peaks of 0.6 ppm and 0.5 ppm + peaks of 1 ppm in the Lang study, and in that of Mueller 0.3 ppm + peaks of 0.6 ppm and 0.4 ppm + peaks of 0.8 ppm. Objective signs of irritation were only observed at 0.5 ppm + peaks of 1 ppm. Because 0.3 ppm + peaks of 0.6 ppm was a consistent NOAEC in both of these investigations this exposure regime is taken forward for derivation of the OEL, TWA with STEL. The recent study (Mueller et al.

ED_014350_00001020-00010

2013) was conducted with hypo- and hyper-sensitive individuals, who showed no difference in sensory irritation sensitivity to FA, but the hypersensitive individuals reported significantly higher effects for olfactory induced symptoms as "perception of impure air".

Based on these experimental studies in human volunteers SCOEL derives an OEL of 0.3 ppm (8 h TWA) with a STEL of 0.6 ppm. As sensory irritation is a concentration rather than a cumulative dose-driven effect, a STEL value is appropriate. This OEL based on sensory irritation will also protect workers from undue annoyance and discomfort at the workplace.

Ad (b): The OEL of 0.3 ppm derived from human volunteer studies is supported by data in experimental animals. The histopathological NOAEC for nasal effects of FA in rats and monkeys is 1 ppm and for regenerative cell proliferation in rats is 2 ppm. Preventing these effects will also prevent nasal cancer. As a strong support, toxicokinetic studies suggest that at an exposure level of 1 ppm the local intracellular concentration of formaldehyde is dominated by the internal (naturally produced) FA. Backed by this finding, SCOEL considers an uncertainty factor of 3 to be sufficiently protective. This supports the proposed OEL (8h-TWA) of 0.3 ppm.

As a result of the predominantly local effects of FA, a "skin" notation is not required. FA is a well-known contact allergen to the skin (skin sensitizer). A notation sensitisation (Dermal) is therefore added. Against the background of a widespread use, respiratory sensitization has been reported only occasionally, and therefore the designation as respiratory sensitizer is not warranted.

A biological limit value (BLV) or biological guidance value (BGV) is not proposed.

For additional details, which were considered in the OEL derivation by SCOEL, see chapter 7.11.

ED_014350_00001020-00011

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR FORMALDEHYDE

Recommendation Report

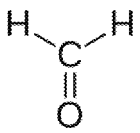
1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name: formaldehyde

Synonyms: methanal, oxomethane, oxymethylene, methylene oxide, methyl aldehyde

Molecular formula: CH_2O

Structural formula:



EC No.:	200-001-8
CAS No.:	50-00-0
Molecular weight:	30.03 g/mol
Melting point:	-92°C
Boiling point:	-21°C
Conversion factor: (20 °C, 101.3kPa)	1 ppm = 1.23 mg/m^3

ED_014350_00001020-00012

2. EU Harmonised Classification and Labelling

The most recent information about the status of the EU harmonised classification and labelling for formaldehyde was provided by ECHA (2012) and is summarized below in Table 1.

Table 1: Classification of formaldehyde according to the CLP hazard classes and/or categories (Article 37(4) of the Regulation (EC) No 1272/2008), according to Directive 67/548/EEC and to the GHS (ECHA, 2012)

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	**CLP**	**DSD**	**GHS**
	Acute Tox. 3 – H331	T; R23/24/25 (SCL: T ≥ 25%, 5%≤Xn<25%)	
	Acute Tox. 3 – H311		Dgr
	Acute Tox. 3 – H301		GHS05
	Skin Corr. 1B; H314: C ≥ 25 % Skin Irrit. 2; H315: 5 % ≤ C < 25 % Eye Irrit. 2; H319: 5 % ≤ C < 25 % STOT SE 3; H335: C ≥ 5 %	C; R34 (SCL: C 25%, 5%≤Xi; R36/37/38<25%)	
	Skin Sens. 1; H317: C ≥ 0,2 %	R43 (SCL of 0.2%)	
	Muta 2 – H341	Muta cat. 3; R68	GHS06
	Carc. 1B – H350	Carc. Cat. 2; R49	GHS08
	Notes B, D		

3. Chemical Agent and Scope of Legislation

Formaldehyde is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Formaldehyde is also a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this legislation.

ED_014350_00001020-00013

4. Existing Occupational Exposure Limits

Occupational exposure limits for Formaldehyde exist in a number of countries, as shown in table 2 below.

Table 2: Existing OELs for formaldehyde; adapted from the GESTIS database (GESTIS, 2015).

	TWA (8 hrs)		STEL (15 min)		
EU-countries	ppm	mg/m³	ppm	mg/m³	References
Austria	0.5	0.6	0.5	0.6	GKV (2011)
Belgium			0.3	0.38	Belgium (2014)
Denmark	0.3	0.4	0.3	0.4	BEK (2011)
Finland	0.3	0.37	1	1.2	Finland (2012)
France	0.5		1		INRS (2012)
Germany (AGS)	0.3	0.37	0.6	0.74	BAUA (2006)
Germany (DFG)	0.3	0.37	0.6	0.74	DFG (2015)
Hungary		0.6		0.6	Hungary (2000)
Ireland	2	2.5	2	2.5	HSA (2011)
Latvia		0.5			n.r.
Norway	0.5	0.6	1	1.2	Norway (2011)
Poland		0.5		1	Poland (2002)
Spain			0.3	0.37	INSHT (2010)
Sweden	0.3	0.37	0.6	0.74	SWEA (2011)
The Netherlands		0.15		0.5	NED (2007)
United Kingdom	2	2.5	2	2.5	HSE (2011)
Non-EU-countries					
Australia	1	1.2	2	2.5	Safe Work Australia (2011)
Canada (Ontario)			1		Ontario Ministry of Labour (2013)
Canada (Québec)			2	3	IRSST(2010)
China				0.5	n.r.
Japan	0.1	0.12			JSOH (2015)
New Zealand	0.5 0.33*		1		HS (2013)
Singapore			0.3	0.37	n.r.
South Korea	0.5	0.75	1	1.5	n.r.

Switzerland	0.3	0.37	0.6	0.74	SUVA (2015)
USA (NIOSH)	0.016		0.1		NIOSH (2007)
USA (OSHA)	0.75		2		OSHA (2006)

* 12 hour shift; n.r.: no specific reference

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Formaldehyde is a ubiquitous compound in the environment (IARC, 2012). Being a simple, one-carbon molecule that is rapidly metabolised, it is endogenously produced, and is also formed through the metabolism of many xenobiotic agents. It occurs in most life forms, including humans. It has been detected in indoor and outdoor air; in treated drinking water, bottled drinking water, surface water, and groundwater; on land and in the soil; and in numerous types of food (NTP, 2010).

Formaldehyde is present in outdoor air as a result of its formation from the combustion of organic materials (e.g., in automobiles, forest fires, and power plants), its formation from the breakdown of hydrocarbons in the air, and releases from industrial facilities. According to (IARC, 2012), automobile exhaust is a major source of formaldehyde in ambient air. In indoor air, it is present as a result of off-gassing from formaldehyde-containing materials such as wood products, carpets, fabrics, paint, and insulation, and it is formed from combustion sources such as wood stoves, gas stoves, kerosene heaters, open fireplaces, and furnaces, through cooking, and in cigarette smoke (NTP, 2010).

Formaldehyde is a high-production-volume chemical with a wide array of uses. Predominantly it is used as a chemical intermediate. According to IARC (2012) formaldehyde is used mainly in the production of various types of resin. Phenolic, urea, and melamine resins have wide uses as adhesives and binders in the wood-production, pulp-and-paper, and the synthetic vitreous fibre industries, in the production of plastics and coatings, and in textile finishing. Polyacetal resins are widely used in the production of plastics. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol, 4,4′-methylenediphenyl diisocyanate, penta-erythritol, and hexamethylenetetramine. Formaldehyde is used directly in aqueous solution (known as formalin) as a disinfectant and preservative in many applications.

ED_014350_00001020-00015

5.2. Production and use information

Formaldehyde has been produced commercially since 1889 by catalytic oxidation of methanol. Currently, the two predominant production processes are a silver catalyst process and a metal oxide catalyst process (Bizzari, 2007). According to IHS (2012) formaldehyde is usually produced close to the point of consumption since it is fairly easy to make, is costly to transport and can develop problems associated with stability during transport. As a result, world trade in formaldehyde is minimal.

The European Union is the second largest producer of formaldehyde after Asia, producing over 3.6 million tonnes of formaldehyde each year which accounts for about 30% of global production (EU capacity in 2009). Annual sales of formaldehyde-based chemicals in the EU are roughly €9.5 billion a year, and 22 of the 27 EU Member States manufacture formaldehyde. Germany is the largest formaldehyde producer in the EU, followed by Italy, Spain, the Netherlands and the UK (SRI, 2009).

According to IHS (2012) urea-, phenol- and melamine-formaldehyde resins (UF, PF and MF resins) accounted for about 63% of world demand in 2011; other large applications include polyacetal resins, pentaerythritol, methylene-bis(4-phenyl isocyanate) (MDI), 1,4-butanediol and hexamethylenetetramine. China is the largest single market for formaldehyde, accounting for about 34% of world demand in 2011; other large markets include the United States, Canada, Brazil, Germany, the Netherlands, Spain, Italy, Belgium, Poland, Russia, Japan and the Republic of Korea. China is forecast to experience fast growth rates (around 7% per year) and significant volume increases in demand for 37% formaldehyde during 2011–2016. World consumption is forecast to grow at an average annual rate of almost 5% during 2011–2016. Continuing significant-to-rapid demand growth in Asia (mainly China) for most applications will balance out moderate growth in North America, Western Europe, Africa and Oceania. Central and South America, the Middle East, and Central and Eastern Europe are forecast to experience significant growth in demand for formaldehyde during 2011–2016, largely as a result of increased production of wood panels, laminates, MDI and pentaerythritol (Tang 2009; IHS, 2012).

5.3. Occupational Exposure

Occupational exposure to formaldehyde occurs in a wide variety of occupations and industries. IARC (2012) refers to CAREX as an international information system on occupational exposure to known and suspected carcinogens based on data collected in the European Union (EU) from 1990 to 1993. The highest continuous exposures (2-5 ppm; 2.5–6.1 mg/m^3) were measured in the past during varnishing of furniture and wooden floors, in the finishing of textiles, in the garment industry, in the treatment of fur, and in certain jobs within manufactured board mills and foundries. Short-term exposures to high levels (3 ppm and higher; ≥ 3.7 mg/m^3) were reported earlier for embalmers, pathologists, and paper workers.

For more detailed information, reference can be made to IARC (2012).

5.4. Routes of Exposure and uptake

Formaldehyde can be inhaled, ingested or absorbed through the skin. Inhalation is considered to be the main route of exposure of exogenous formaldehyde (Checkoway et al. 2012). Almost no data are available in the literature on dermal exposure (Sax and Bennett 2004). As critical effects associated with formaldehyde exposure are directly linked to the contact surface, the oral pathway may not be negligible.

Estimates of daily formaldehyde intake by six age groups of the general population in Canada were carried out to determine the relative contributions from different media (Sexton and Adgate 2004). These calculations indicate that daily formaldehyde intake via

ED_014350_00001020-00016

inhalation is much lower than for intake from food (WHO, 2010). According to JRC (2005) and considering exclusively inhalation, indoor exposure contributes up to 98% to the integrated exposure of the general population (considering time–activity patterns and daily inhalation volume).

6. Monitoring Exposure

According to DECOS (2003) and NEG (2003) the most widely used methods for the determination of formaldehyde in air samples are based on photometric measurements. The sampling method depends on the medium in which formaldehyde is to be determined. WHO (1989) reported a number of different methods for determination of formaldehyde, using spectrophotometric, colourimetric, fluorometric, high performance liquid chromatographic (HPLC), polarographic, gas chromatographic, infrared, and visual analytical methods. A more recent review is provided by Salthammer (2010). Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). Aqueous or 50% 1-propanol solutions are also used for formaldehyde sampling. For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolene hydrazine (MBTH), chromotropic acid or 2,4-dinitrophenylhydrazine (DNPH) are generally used as the absorbing solution. For passive sampling sodium bisulphite, triethanolamine and DNPH are used and sorbents such as silica gel, aluminium oxide and activated carbon, sometimes specially treated, may be useful for taking samples at the workplace. Among the available methods, the DNPH method is frequently used for the simultaneous analysis of formaldehyde, other aldehydes, and ketones. It is described in U.S. EPA Method TO-11A (U.S. EPA, 1999). ASTM D5197 (ASTM, 2009) is accepted as an international standard by ISO (2011) and is recommended by the MAK Commission (Schmitz and Tschickardt, 2002) for monitoring occupational exposures.

Schmitz and Tschickardt (2002) describe the application of "MAK Method 2" as a preferred method, which is based on the DNPH method. Air from the workplace is drawn with a sampling pump through silica gel cartridges impregnated with DNPH. The airborne aldehydes and ketones are transformed into the corresponding hydrazones. After desorption with acetonitrile, qualitative and quantitative determination is carried out by using high performance liquid chromatography (HPLC). Performance characteristics of this method, specifically for formaldehyde, were reported by Schmitz and Tschickardt (2002) as follows:

Precision:

Standard deviation (rel.)	sw = 5.0, 1.7 and 3.9 % at concentrations of 150, 600 and 1200 µg of formaldehyde per m^3
Mean variation	u = 11.9, 4.3 and 9.9 % at concentrations of 150, 600 and 1200 µg of formaldehyde per m^3 air and for n = 6 determinations

Detection limit:

11 µg Formaldehyde per m^3 air (for a sample volume of 6 l air)

Recovery rate: 1.01 (101%)

Recommendation for sampling:

Sampling time: 1 h
Sample volume: 6 l
Sampling rate: 100 ml min^{-1}

ED_014350_00001020-00017

In addition to this "Method 2", the MAK Commission (Kuck 1993) also recommends "MAK Method 3", which is based on voltametry in combination with differential pulse polarography (DPP) as the analytical principle. Beyond these Methods 2 and 3 by the MAK Commission, several other methods have been recommended for monitoring occupational exposure to formaldehyde by NIOSH, OSHA, among others competent institutions. A non-exhaustive listing of such methods is provided below:

Passive sampling methods:

- **OSHA Method No 1007** (OSHA 2005). Target concentration is in the range of 0.75 ppm (0.92 mg/m^3). Diffusive samples are collected by exposing either Assay Technology ChemDisk Aldehyde Monitor 571 (ChemDisk-AL), SKC UMEx 100 Passive Sampler (UMEx 100), or Supelco DSD-DNPH Diffusive Sampling Device (DSD-DNPH) to workplace air. Samples are extracted with acetonitrile and analysed by LC using a UV detector. In the UK, **HSE-MDHS 78 (1994)**, a method based on the same principle, has been replaced by **HSE-MDHS 102 (2010)**; in this method the samplers are solvent desorbed into acetonitrile and the aldehyde derivatives analysed using HPLC with a photodiode array detector (PDA). Separation is achieved using a C18 column (3.9 × 300 mm) maintained at a temperature of 50 °C.

- **OSHA method ID-205**(OSHA 1985). A modified chromotropic acid procedure is used. Sample filters are desorbed using deionized water. Solutions are acidified, and chromotropic acid is added. The color complex formed is analyzed using a UV spectrophotometer at 580 nm. Detection limits are 0.039 ppm (qualitative) and 0.11 ppm (quantitative) at a sampling time of 4 hours. The collection devise is a passive badge monitor containing bisulfite-impregnated paper. The dose range provided by the manufacturer is 0.8 to 72 ppm-h.

Active sampling methods:

- **NIOSH Method 2016, Issue 2, 15th March 2003;** (NIOSH 2003): The working range is 0.015 to 2.5 mg/m^3 (0.012 to 2.0 ppm) for a 15-L sample. This method can be used for the determination of formaldehyde for both STEL and TWA exposures. Sampling is carried out with a cartridge containing silica gel coated with DNPH and extraction via elution with 10 mL of carbonyl-free acetonitrile. Finally the analysis takes place with HPLC, UV detection. In addition to NIOSH Method 2016, INRS (INRS 2005) and AFNOR have developed two methods based on the same principle: **INRS Metropol 001/V01(2005)** and **AFNOR NFX 43-264 (2002)**.

- **NIOSH Method 2541, Formaldehyde by GC, Issue 2, 15th August 1994**; (NIOSH 1994a): The working range is 0.24 to 16 ppm (0.3 to 20 mg/m ^{3}) for a 10-L air sample. The method is suitable for the simultaneous determinations of acrolein and formaldehyde. Sampling is carried out in a solid sorbent tube (10% (2-hydroxymethyl) piperdine on XAD-2, 120 mg/60 mg). Desorption takes place in 1 mL toluene; 60 min ultrasonic and the analysis is carried out using GC/FID or NPD. A similar method, **OSHA 52 (1989)** has been proposed by OSHA (1989).

- **NIOSH Method 3500, Formaldehyde by VIS, Issue 2, 15th August 1994** (NIOSH 1994b): The working range is 0.02 to 4 ppm (0.025 to 4.6 mg/m^3) for an 80-L air sample. This is the most sensitive formaldehyde method in the NIOSH Manual of Analytical Methods and is able to measure ceiling levels as low as 0.1 ppm (1 5-L sample). It is best suited for the determination of formaldehyde in

ED_014350_00001020-00018

area samples. Sampling takes place using filters and impingers (1-µm PTFE membrane and 2 impingers, each with 20 mL 1% sodium bisulfite solution). Being a chromotropic method the colour development takes place in a chromotropic acid (+ sulfuric acid; absorbance at 580 nm) while the analysis takes place with visible absorption spectrometry. A method based on a similar principle, **INSHT-MTA/MA-018/A89(1989),** has been proposed by INSHT (1989).

The above mentioned methods have been evaluated by AFSSET (2008). On this basis, they recommended NIOSH method 2016 and INRS Metropol 001/V01 (2005) for active sampling and OSHA method 1007 for passive sampling. These methods show sufficient limits of detection and quantification and can be executed with readily available materials in the laboratories.

7. HEALTH EFFECTS

As a result of its reactivity in target tissues with direct contact with the substance, FA causes local irritation, acute and chronic toxicity and has genotoxic and cytotoxic properties (DECOS, 2003; NEG, 2003; DFG, 2014).

Studies with volunteers yielded threshold concentrations for odour perception of less than 0.5 ppm, for eye irritation of 0.5 to 1 ppm and for nose and throat irritation of l ppm; sensory eye irritation was observed in some cases also at lower concentrations, predominately based on subjective symptoms. In workers exposed long-term to FA at the workplace, lesions were observed in the nasal mucosa even at average exposure concentrations below 1 ppm. But it was concluded that the studies reporting such effects would not allow defining exposure concentrations or peaks above which the histopathological nasal lesions may occur (DFG, 2014). More recent studies in this respect are not available. The experimental no-effect-level of sensory irritation in BALB/c mice has been determined to be 0.3 ppm (Nielsen et al., 1999).

FA causes sensitisation of the skin and there are some reports indicating also to bronchial asthma (e.g. Lemière et al. 1995).

Studies reporting induction of asthma have been reviewed by DFG (2014) concluding "that FA is responsible for allergic asthmatic conditions only in very rare cases in spite of the wide range of possibilities of exposure" and that a designation as an asthma inducing agent would not be justified.

7.1. Toxicokinetics, Absorption, Distribution, Metabolism, Excretion (ADME)

Several mechanisms are involved in the inactivation of FA. The inhaled hydrophilic gas dissolves first of all in the layer of mucus covering the nasal epithelium; reactions with components of the mucus (Bogdanffy et al. 1987) and mechanical clearance of the mucus represent the first barrier. From a certain exposure concentration mucociliary clearance is impaired.

As the cytotoxic and genotoxic FA is a normal intermediary metabolic constituent of all cells, efficient intracellular defence mechanisms exist. The most important among these mechanisms is formaldehyde dehydrogenase (FDH) that rapidly oxidises FA to formic acid after a non-enzymatic reaction of FA with reduced glutathione to S-hydroxymethylglutathione. Formic acid then enters into the physiological C_1 pool and may be finally oxidised to CO_2 (Yu et al 2015).

ED_014350_00001020-00019

7.1.1. Human data

As formaldehyde dehydrogenase (FDH; ADH 5) is the major detoxification enzyme, the question arises whether polymorphism of this enzyme may render subgroups of the normal population specifically sensitive to FA toxicity. Former studies with in total more than 1000 samples from human donors did not find any indication for polymorphism on the protein level (Castle and Board, 1982; Uotila and Koivusalo, 1987; Benkmann et al., 1991). Hedberg et al. (2001) found a polymorphism in promoter region with reduced transcriptional activity in vitro. As the biological meaning of these polymorphisms for FA related toxicity remained unclear, further studies were carried out, as follows.

Just et al. (2011) investigated 3 polymorphisms in the blood of healthy German volunteers. The polymorphism described by Hedberg et al. (2001) was not detected in 150 subjects and another polymorphism described in literature was not detected in 70 subjects. A third polymorphism was identified in 105 subjects: 43 were heterozygous, 46 homozygous for one allele and 16 homozygous for the other allele. As the comet assay with blood samples of homozygous subjects showed no difference in strand breaks or DNA-protein-crosslink (DPX) formation, no influence on in vitro genotoxicity of FA, no biologically relevant polymorphisms of the FDH gene could be identified. FA exposure did not lead to alterations of FDH expression in human volunteers at concentrations up to 0.7 ppm or at 0.4 ppm plus peaks of 0.8 ppm (Zeller et al, 2011a) [for details of exposure see Mueller et al, 2013] or in vitro with human A549 lung cells (Speit et al, 2010) or nasal epithelial cells (HNEC) (Neuss et al, 2010b).

No differences for inter-individual susceptibility could be identified with 30 male smokers, 30 female non-smokers and 30 school children when leukocytes were incubated with FA. The endpoints studied included in vitro formation and removal of DPX by the Comet assay, in vitro induction and persistence of SCE and expression of mRNA levels of the FDH gene by real-time PT-PCR. In addition there was no association of GSTM1 and GSST1 polymorphism with in vitro genotoxicity (Zeller et al., 2012). When the leukocytes of the volunteers of the Mueller et al. (2013) study were subjected to the same in vitro battery of tests no differences were identified for the subgroups hyper- and hyposensitive persons to CO_2 induced nasal irritation (Zeller et al., 2011b).

Santovito et al. (2011) did not observe an influence of different GST genotypes on the level of chromosomal aberrations in pathology workers, similar to Costa et al. (2008) for the endpoints of micronuclei, SCE and in the comet assay and to Ladeira et al (2013) for micronuclei. A slightly different result was obtained in a field study with workers in plywood industries by Jiang et al. (2010). They observed in peripheral blood lymphocytes of the workers an increased tail moment in the comet assay and increased micronuclei by the cytokinesis-block micronucleus assay. The effect in the comet assay was slightly higher in the GSTM1 subgroup and in the comet assay in workers with the GSTP1 Val allele as compared to those with non-null or the wild-type allele. No effects were noted for the subgroups of GSTT1 null *vs.* non-null workers. The authors suggested that polymorphism of GST genes may modulate systemic genotoxicity of FA, but no explanation was given for the divergent results obtained by the comet and micronucleus assay.

In summary, these data show that there are no major inter-individual differences in genetic variability of FDH (protein level) and the FDH gene (gene expression), for ex vivo formation/removal of DPX and SCE or of GST polymorphism on ex vivo genotoxicity.

Garcia et al. (2009) modelled the nasal cavity by MRI or CT scans of 5 adults and 2 children. Airflow was simulated for breathing at rest and the dosimetry for water-soluble, reactive chemicals, like FA was simulated. Most of the gas was absorbed in anterior nasal passage and the inter-human variability related to mass impacted/time/surface area was 1.6-fold without a significant difference between children and adults.

ED_014350_00001020-00020

7.1.2. Animal data

In inhalation studies with rats exposed to 15 ppm, the mucociliary function in the frontal nasal region was inhibited and marked mucostasis was observed. After exposure to a level of 6 ppm only certain areas were affected. After exposure to a level of 2 ppm minimal changes in the mucus flow rate were observed, whilst 0.5 ppm had no effect (Morgan et al. 1986). With sufficiently high exposure concentrations, a concentration gradient of free FA was established within the layers of the nasal epithelium. Under these circumstances, in the fully differentiated cells near the surface, the actual concentration is higher than in the lower-lying proliferating stem cells. In the rostral third of the respiratory epithelium, however, the epithelium consists of only two cell layers with few basal cells (Hermann, 1997). In the epithelial cells there are several ways inactivation can take place. Direct reactions with protein and RNA in the cytosol probably remove a large amount of free FA (Casanova-Schmitz et al., 1984). The molecule may enter the C_1 pool of cell metabolism, and there is effective GSH-dependent oxidation by FDH (Heck and Casanova-Schmitz, 1984; Heck and Casanova, 2004).

FA was not found to pass the airway epithelium in rats and monkeys, and entering the blood compartment (see 7.9.1.)

7.1.3. In vitro data

Cultivation of human nasal epithelial cells with a high concentration (300 µM) of FA for one hour caused DNA protein crosslinks (DPX) in the cells; the FA concentration in the medium decreased only by about 10% during the 1-hour exposure. Replacing the medium by a medium without FA showed no release of FA from the epithelial cell into the new medium. Neither did co-cultivation with lymphocytes show DNA damage in the Comet assay in the lymphocytes after change of the medium (Neuss et al., 2010a,b). Similarly, a 1-hour exposure of the human lung epithelial cell line (A549) caused sister chromatide exchanges (SCE) in the cells with ≥ 100 µM FA. Change of the medium and co-cultivation with V79 Chinese hamster cells showed no SCE in the V79 cells (Neuss and Speit, 2008). Thus, FA liberation was not detected from any of the epithelial cells.

7.1.4. Biological monitoring

The concentration of endogenous FA in human blood is about 2-3 mg/l; similar concentrations are found in monkeys and in rats. Exposure of humans, monkeys or rats to FA by inhalation has not been found to alter the concentration of FA in the blood. The average level of formate in the urine of people not occupationally exposed to FA is 12.5 mg/l and varies considerably both within and between individuals. As stated by IARC (2006), no significant changes of urinary formate were detected after exposure to 0.4 ppm FA for up to 3 weeks in humans. On the other hand, recently an increased urinary excretion of formic acid was noted in workers exposed to FA below 0.2 ppm (Peteffi et al. 2015, 2016). In essence, more studies appear required on this issue.

7.1.5. Toxicokinetic modelling

The kinetics of DNA-protein cross-link formation by inhaled formaldehyde in the nose were modelled by Casanova et al (1991). This model included both saturable and non-saturable elimination pathways and described regional differences in DNA binding as having an anatomical basis. There was significant overlap between model-predicted and fitted curves. Concentrations of cross-links produced in the nasal mucosa of adult men were predicted based on experimental data in rats and monkeys. The results suggested that formaldehyde would generate lower concentrations of cross-links in the nasal mucosa of humans than of monkeys, and much lower concentrations in humans than in rats. The rate of formation of DNA-protein cross-links was regarded as a surrogate for the delivered concentration of formaldehyde. The authors claimed that their model decreased the uncertainty of human cancer risk estimates for formaldehyde derived by

ED_014350_00001020-00021

interspecies extrapolation by providing a more realistic measure of the delivered concentration at critical target sites.

7.2. Acute toxicity

7.2.1. Human data

As the primary effect of formaldehyde is local irritancy, the relevant data are presented in chapter 7.4.1.

7.2.2. Animal data

Studies of the sensory irritation caused by FA in mice and rats are described in chapter 7.4.2.

7.3. Specific Target Organ Toxicity/Repeated Exposure

Studies of the subchronic and chronic toxicity of inhaled FA have been documented by DFG (2000) and jointly by DECOS (2003) and the Nordic Expert Group (NEG, 2003). In all animal experiments, the most noticeable toxic effects of FA were observed in the upper respiratory tract; these effects have been investigated in numerous studies that are described in chapter 7.4.1.

7.3.1. Human data

There are reports on cases of systemic (*e.g.*, anaphylaxis) or, much more often, localized (*e.g.*, contact dermatitis) allergic reactions attributed to the formaldehyde (or formaldehyde-containing resins) present in household and personal care (and dental) products, clothing and textiles, bank note paper, and medical treatments and devices. Also, in exposed persons mild to moderate sensory eye, nose, and throat irritation was experienced (for details, see IPCS 2002).

7.3.2. Animal data

In rats exposed to FA concentrations of 10 ppm, daily for 6 hours on 5 days a week, rhinitis, hyperplasia and squamous metaplasia of the respiratory epithelium of the nasal mucosa were described in all studies. In rats exposed to 1.0 ppm for 2 years no histopathological changes were observed (no observed adverse effect concentration, NOAEC; Woutersen et al., 1989). From concentrations of 2 ppm, rhinitis, epithelial dysplasia and even papillomatous adenomas and squamous metaplasia of the respiratory epithelium of the nose were found, from 6 ppm squamous cell carcinomas (Kerns et al, 1983; Swenberg et al, 1980). At this concentration also the cell proliferation rate in the nasal mucosa was increased transiently, and from 10 ppm increased permanently (Monticello et al, 1996).

Uninterrupted exposure of rats for 8 hours/day ("continuous") was compared with 8 exposures for 30 minutes followed by a 30-minute phase without exposure ("intermittent") in two 13-week studies with the same total dose. Effects were seen only after intermittent exposure to FA concentrations of 4 ppm, but not after continuous exposure to 2 ppm. The authors concluded that the toxicity in the nose depends on the concentration and not on the total dose (Wilmer et al, 1989). In mice exposed to FA concentrations of 2.0, 5.6 or 14.3 ppm for 2 years (6 hours/day, 5 days/week), rhinitis

ED_014350_00001020-00022

and epithelial hyperplasia was observed, from 5.6 ppm dysplasia, metaplasia and atrophy. Squamous cell carcinomas were observed only after concentrations of 14.3 ppm (Kerns et al, 1983).

In hamsters exposed to FA concentrations of 10 ppm (5 hours/day, 5 days per week) for life, survival was reduced and the incidence of hyperplasia and metaplasia (4/88, 5 %) was slightly increased, but not that of tumours (Dalbey, 1982).

In Cynomolgus monkeys exposed almost continuously to FA concentrations of 0.2, l or 3 ppm for 26 weeks, metaplasia and hyperplasia were observed in 1/6 and 6/6 animals of the 1 and 2 ppm groups, respectively. In the animals exposed to concentrations of 0.2 ppm, no histopathological changes were found (Rusch et al, 1983a, 1983b).

Reduced body weight gains were reported in rats exposed to FA concentrations from 10 ppm for 6 hours a day in a 13-week inhalation study (Woutersen et al, 1987) and in those exposed to concentrations from 5.6 ppm in a 2-year inhalation study (Kerns et al, 1983; Swenberg et al., 1980). In mice, reduced body weight gains were found in a 13-week inhalation study only at concentrations from 20 ppm. Other systemic effects were not observed in these studies. Only in a 26-week inhalation study with continuous exposure (22 hours a day, 7 days a week) were reduced absolute and relative liver weights observed from concentrations as low as 3 ppm (in addition to reduced body weight gain and lesions in the nasal region) (Rusch et al., 1983a, 1983b).

The findings in rats were reconfirmed after exposure of male F344 rats to concentrations of 0, 0.5, 1, 2, 6, 10 and 15 ppm (6 h/d, 5 d/week over 4 weeks). At 10 or 15 ppm clear site-specific pathological changes (focal epithelial degeneration, inflammation and squamous metaplasia) were observed in a decreasing gradient (anterior to posterior) (Speit et al, 2011a).

A study related to the possible induction of lympho-haematopoetic neoplasms has been carried out in Fischer-344 rats and B6C3F1 mice at exposure concentrations between 0.5 and 15 ppm over 4 weeks (Kuper et al., 2009). Nasopharynx-associated lymphoid tissues (NALT) and upper-respiratory tract-draining lymph nodes were studied by standard histopathology and immunohistochemistry for cell proliferation. The only effect noted was simple hyperplasia and increased proliferation rate of the lympho-epithelium of rats at 15 ppm. Therefore the study did not support the hypothesis that FA may induce such systemic neoplasms by reaction with local lymphoid cells.

7.3.3. In vitro data

Cytotoxicity of formaldehyde has been studied in several in vitro models. It was verified that formaldehyde may enter cells as such and then elevates the endogenous formaldehyde concentration (Ke et al. 2014). Cell models of human nasal epithelial cells are being developed for testing of gaseous formaldehyde toxicity (Wang et al. 2014).

7.4. Irritancy and corrosivity

FA is classified as Skin Corrosive cat 1B (H314) according to CLP.

7.4.1. Human data

A recent study by Berglund et al. (2012) determined the average (P50) absolute odour threshold (corrected for "false alarm") of FA to 0.1 ppm (Range: 0.02-0.5 ppm). Overall, the odour response of FA occurs below observed toxicological effects.

In itself, an odour cue can increase reporting of symptoms (e.g. headache, nausea, and eye and throat irritation) due to stress-related perceptions, triggered by belief about potential toxicological risks; this is especially prominent among individuals with

ED_014350_00001020-00023

"environmental worry" and "negative affectivity", but symptom reporting may also be influenced by belief about (positive, neutral or negative) health effects of an odour (Greenberg et al, 2013; Nimmermark, 2004; Dalton, 2003; Shusterman, 2001; Shusterman et al, 1991 and references therein).

Studies with the controlled exposure of volunteers must be distinguished from epidemiological studies of persons exposed at the workplace or under certain environmental conditions. The most reliable data are obtained in controlled studies with volunteers. Studies of persons exposed at the workplace are less suitable for making quantitative statements, mainly because of uncertain levels of exposure. Approximately 150 scientific papers (animal studies, human volunteer and occupational studies) on FA effects were evaluated by a panel of independent experts convened by the Industrial Health Foundation (IHF; Paustenbach et al., 1997). The data were indicative of a relatively wide individual susceptibility to irritation from FA. Data available for eye irritation from a total of 17 volunteer studies had been compiled and evaluated. The experts concluded that between 0 and 0.3 ppm there is no increase in eye irritation above the general background level of about 10-20%, and irritation below 0.3-0.5 ppm FA was too unreliable to attribute the irritation solely to FA. A concentration-effect curve was constructed showing that at 0.5–1 ppm, exposure for up to 6 hours can produce eye irritation in 5–25 % of the exposed persons, although responses below 20% were often not considered attributable to FA alone. It was concluded, based on the controlled human and epidemiological studies, that at 0.3 ppm or less no irritation attributable to FA should occur, if people are exposed up to 8 hours per day. Significant increases in eye irritation are reported, however, only at concentrations of at least 1 ppm, which is the reason that this concentration is often regarded as a ceiling value (Paustenbach et al., 1997). Similar reviews with a partly overlapping database were carried out by Bender (2002) and Arts et al. (2006) basically coming to the same conclusions. It must be taken into consideration that apart from one study all the others reviewed only relied on reporting of subjective symptoms for sensory eye irritation.

The question of a threshold for chemosensory irritation was experimentally addressed by Lang et al. (2008). Twenty-one volunteers (11 males, 10 females) were examined over a 10-week period using a repetitive design. Each subject was exposed to 10 exposure conditions on 10 consecutive working days, each for 4 hours. FA exposures were 0 (control), 0.15, 0.3 and 0.5 ppm, respectively. Also, a group with 0.3 ppm FA exposure with 4 peaks, each with a duration of 15-min, at 0.6 ppm and a group exposed at 0.5 ppm with 4 peaks at 1 ppm were included. Furthermore, ethyl acetate was used to mimic or mask the odour of FA. Thus, ethyl acetate alone (another control group), and 0.3 and 0.5 ppm FA groups were added ethyl acetate, as was a group with 0.5 ppm FA with peaks at 1 ppm. The ethyl acetate concentrations were 12–16 ppm. During exposure, subjects had to perform three cycle ergometer units at 80 watts for 15 min. Apart from reporting of subjective symptoms for irritation, measurements were related to objective effects of FA exposures as conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function and reaction times. Blinking frequency and conjunctival redness (ranging from slight to moderate) were significantly increased at 0.5 ppm with peak exposures, but no increase was observed at 0.5 ppm alone. FA had no effect on the other objective parameters. Results of subjective ratings (score for total symptom, eye irritation, nasal irritation, olfactory symptoms, respiratory irritation, and annoyance) were highly variable as indicated from the SDs and the maximum scores; the prerequisite (normal distribution) for the ANOVA testing was not reported. The total symptom score was increased only at 0.5 ppm with peaks at 1 ppm. The eye irritation score was increased at 0.3 and 0.5 ppm FA compared to the 0 ppm FA group; the mean symptom rating was below "slight". However the increases were not exposure-dependent and they were similar to that in the ethyl acetate (odour) control group. The 0.5 ppm group with peak exposures had significantly higher score than the two control groups; eye irritation was on average less than "somewhat". Nasal irritation was similar in the FA groups, 0.3, 0.3 with peaks and 0.5 ppm alone, and the ethyl acetate (odour) control group and not different from the 0 ppm control group; the 0.5 ppm FA group with peaks had a significantly higher score than the two control groups. An exposure-dependent

significant respiratory irritation score was only reported at the 0.5 ppm with peaks, but this was not significantly different from the ethyl acetate (odour) control group; the mean symptom rating was below "slight". Olfactory symptom scores were increased in ≥ 0.3 ppm FA exposure groups compared with the 0 ppm control group. The ratings in the 0.3 group with peaks, the 0.5 group alone and the 0.5 ppm group with peaks were similar to the ethyl acetate control group. Annoyance was increased in the 0.3 group with peaks, the 0.5 group and the 0.5 ppm group with peaks compared with the 0 ppm control group. When negative affectivity was introduced as a covariate, the level of 0.3 ppm was no longer an effect level, but 0.5 ppm with peaks of 1.0 ppm was. The authors concluded that eye irritation was the most sensitive parameter recorded, and that the no-observed-adverse-effect level for objective eye irritation was 0.5 ppm. The similar value was observed for subjective eye irritation if odour bias and negative affectivity were included in the evaluation. The LOAEC was 0.5 ppm with peaks at 1 ppm. No sex differences were noted.

In view of open questions resulting from this study, a new exposure study in volunteers was conducted to examine chemosensory effects of FA in so-called "hyposensitive" and "hypersensitive" persons (Mueller et al, 2013). Forty-one male volunteers (aged 32 years ± 9.6) were exposed for 5 days (4 hours per day) in a randomised schedule to the control condition (0 ppm) and to FA concentrations of 0.5 and 0.7 ppm and to 0.3 ppm with peak exposures of 0.6 ppm, and to 0.4 ppm with peak exposures of 0.8 ppm, respectively. Peak exposures were carried out four times a day over a 15-min period. During exposure, subjects had to perform four cycle-ergometer units at 80 watts for 15 min. Subjective pain perception induced by nasal application of carbon dioxide (CO_2) served as indicator for sensitivity to sensory nasal irritation. The division between "hypersensitive" and "hyposensitive" subjects was based on the median in sensitivity towards the irritating effect of CO_2. The following parameters were examined before and after exposure: subjective rating of symptoms and complaints (Swedish Performance Evaluation System, SPES), conjunctival redness, eye-blinking frequency, self-reported tear film break-up time and nasal flow rates. In addition, the influence of personality factors on the volunteer's subjective scoring was examined (Positive And Negative Affect Schedule, PANAS). FA exposures to 0.7 ppm for 4 hours and to 0.4 ppm for 4 hours with peaks of 0.8 ppm for 15 min caused no significant sensory irritation of the measured conjunctival and nasal parameters (conclusion by the authors). In all groups, the mean sum score of the individual symptoms, the eye irritation score and the nasal irritation score were within a range of less than 2.5 mm on a 100-mm Visual Analogue Scale (VAS). No differences between hypo- and hypersensitive subjects were seen. Statistically significant differences were noted for olfactory symptoms, especially for the "perception of impure air". These subjective complaints were more pronounced in hypersensitive subjects. But after a detailed analysis the authors concluded that these effects were mainly induced by unpleasant smell and the situational and climatic conditions in the exposure chamber. FA concentrations of 0.7 ppm for 4 hours and of 0.4 ppm for 4 hours with peaks of 0.8 ppm for 15 min did not cause adverse effects related to irritation, and no differences between hypo- and hypersensitive subjects were observed (Mueller et al., 2013). Interestingly, Lang et al. (2008) observed subjective symptoms of eye irritation at concentrations upward of 0.3 ppm, but not Mueller et al. (2013). This was explained by differences in the study populations because the PANAS score for negative affectivity in the Lang study was significantly higher ($p<0.02$) as compared to that in the Mueller study. This finding underlines in as much subjective symptoms may be influenced by personality factors like expectation or anxiety.

The study was accompanied by satellite investigations (Zeller et al., 2011a,b). The results indicated that despite large differences in CO_2 sensitivity (see above), the susceptibility towards nasal irritation was not related to the induction of genotoxic effects (DPX, SCEs) in peripheral blood or the protection of blood cells against FA-induced effects (expression of FDH, repair capacity for FA-induced DPX). There was no correlation between CO_2 sensitivity and the expression of FDH. There was also no close correlation between the various indicators of cellular sensitivity towards FA-induced genotoxic effects, and no subgroups were identified with particular mutagen sensitivity towards FA

(Zeller et al 2011a). Moreover, investigations of potential individual susceptibility of human blood cells towards FA-induced genotoxicity indicated no biologically relevant differences with regard to various indicators of cellular sensitivity to genotoxic effects along with the expression of FDH and genetic polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 (Zeller et al 2012). The authors suggested that a low scaling factor to address possible human inter-individual differences in FA-induced genotoxicity could be reasonable. This is also supported by field studies investigating polymorphisms of glutathione S-transferases (Jiang et al., 2010, Santovito et al., 2011).

7.4.2. Animal data

Studies of the sensory irritation caused by formaldehyde in mice and rats showed the mouse to be markedly more sensitive (Barrow et al., 1983, 1986, Chang et al., 1981; Chang and Barrow, 1984). The concentration, which after short-term exposure leads to a reduction in the respiration rate to 50 % (RD50) in mice, was found to be between 3 and 5 ppm (Chang et al. 1981, Schaper 1993). A clear no-effect level for nasal irritation in mice was found to be at 0.3 ppm (Nielsen et al., 1999). In rats, RD50 values between 10 and 30 ppm have been reported (Cassee, 1995; Cassee et al, 1996; Chang et al, 1981; Chang and Barrow, 1984; Schaper, 1993).

7.4.3. In vitro data

No relevant in vitro data were retrieved.

7.5. Sensitisation

FA is a known human skin sensitizer.

7.5.1. Human data

Against the background of a widespread use, respiratory sensitisation has been reported only in single cases (DECOS, 2003; Nordic Expert Group, 2003) and therefore the designation as respiratory sensitizer is not warranted conforming to the conclusion of the DFG (2014).

Some studies raise the question of immunological effects, especially childhood asthma, (McGwin et al, 2010, Aydın et al, 2013, Costa et al, 2013). Because childhood asthma is not relevant for workplace exposure, the present document does not elaborate on this aspect.

In two studies a possible exacerbation of lung function by FA was tested with adult asthmatic volunteers sensitive to grass pollen or dust mites. FA exposure was followed by inhalation of the allergen. Ezratty et al. (2007) found no deleterious effect of FA exposure (0.5 mg/m^3) on symptoms provoked by grass pollen. On the other hand, Casset et al. (2006) observed that FA at 0.1 mg/m^3 enhanced the bronchial responsiveness in another group of mite-sensitised subjects. Both of these studies were analysed in detail by Wolkoff and Nielsen (2010) in respect of an indoor exposure limit of 0.1 mg/m^3. In spite of the effects described by Casset et al. (2006) they concluded that these findings are not in conflict with such an exposure limit for the general population. Whether higher concentrations may in some cases affect sensitised workers cannot be excluded by this analysis. But Paustenbach et al. (1997) concluded that FA does not induce or exacerbate asthma after having reviewed the literature available at that time including several studies with asthmatics. A similar conclusion was obtained for FA concentrations below 1 ppm (Wolkoff and Nielsen, 2010; Nielsen et al., 2013)

7.5.2. Animal data

Results of studies in laboratory animals have indicated that formaldehyde may enhance their sensitization to inhaled allergens. In female BALB/c mice sensitized to ovalbumin,

the serum titre of IgE anti-ovalbumin antibodies was increased approximately 3-fold in animals pre-exposed to 2.0 mg FA/m^3 for 6 h/day on 10 consecutive days. Similarly, exposure of female Dunkin-Hartley Guinea pigs, sensitized to airborne ovalbumin, to 0.3 mg FA/m^3 produced a significant 3-fold increase in bronchial sensitization, as well as a significant 1.3-fold increase in serum anti-ovalbumin antibodies (IPCS 2002).

7.5.3. In vitro data

No relevant data were retrieved.

7.6. Genotoxicity

Genotoxic and mutagenic effects of FA were found in various in vitro test systems. As a reactive compound, FA reacts with nucleic acids and proteins. Results of in vivo studies are more difficult to evaluate. Of particular importance is the question whether cytogenetic effects can only occur as the result of local exposure or also as the result of the systemic availability of FA.

The available data concerning the genotoxicity of FA have recently been evaluated by RAC (ECHA 2012), based on a comprehensive data compilation in the CLH Report (ECHA 2011). In summary, it was concluded that FA induced mutagenic and genotoxic effects in proliferating cells of directly exposed cell lines. FA was addressed as an in vitro mutagen with a predominantly clastogenic mode of action. Gene mutation tests gave insufficient evidence for induction of gene mutations. Clastogenic effects (such as chromosomal aberrations, increased micronucleus formation and sister chromatid exchanges) as well as genotoxic effects (DPX, DNA adducts) were induced in cultured mammalian and human cells in vitro. FA was also genotoxic in somatic cells at the site of contact, as already addressed by SCOEL in 2008. In vitro experiments with A549 human lung cells did not support the idea that low FA concentrations (up to 75 µM) would enhance the genotoxic activity of different classes of mutagens or might interfere with the repair of DNA damage induced by other mutagens (Speit et al 2014).

Based on the CLH Report (2011) RAC (2012) concluded that FA should be classified as mutagen category 2 ("suspected germ cell mutagen"). This decision was based on the ECHA Guidance to CLP that requires that also the indication of genotoxic effects at sites of contact (here predominantly DPX formation in nasal epithelium) have to be taken into consideration for classification even if a substance is not bioavailable to germ cells like FA.

7.6.1. Human data

Since the publication of the SCOEL Recommendation in 2008, a number of genotoxicity studies in exposed humans have been published. Concerning these studies, a major general point of critique was that most studies were performed on only small numbers of subjects, which makes interpretation difficult (CLH Report 2011). A number of published studies did not include an analytical exposure assessment and can therefore not be evaluated.

7.6.1.1. Systemic

In the DNA of white blood cells from workers exposed to FA (average concentrations determined by personal air sampling: 2.8-3.1 ppm), the incidence of DPX was significantly higher than in control persons ($p = 0.03$). Assuming that FA reaches the blood cells via the lungs, it was suggested DPX be used as a biomarker for exposure to FA (Shaham *et al.* 1996). Because of methodological shortcomings, this study has, however, been heavily criticised (the blood samples were allowed to stand for 3 hours, the intra-individual and analytical variability were not determined, FA-induced DPXs and DNA-protein crosslinks of other genesis were not differentiated (Casanova *et al.* 1996);

ED_014350_00001020-00027

however, a more recent study by the same group has been considered (IARC, 2005) to reveal increased DPX in workers exposed to FA (Shaham et al., 2003).

It has been stated in the CLH Report (2011) that positive genotoxicity results were observed mainly in populations involved in embalming procedures and in pathology workers. More recently further studies became available with larger study populations that warrant an overall assessment of all data on systemic genotoxicity. These publications are summarized in Table 3.

In a study on a small number (n=20) of nurses exposed to cytostatic drugs, anaesthetics, FA and other sterilising gases, elevated sister chromatid exchange counts in blood cells were observed *vs.* a control group. Quantitative exposure data were not given (Santovito *et al* 2014). Therefore, no conclusions may be drawn regarding a specific effect of FA.

Table 3: Systemic genotoxicity in exposed workers

Author	Study group	N: exp./contr.	Exp. Level	Endpoints	Result
Thomson, 1984	Pathology	6/5	1.14-6.93 mg/m³ during tasks lasting over 2-4 h/d; peaks up to >11mg/m³	CA SCE	- -
Bauchinger, 1985	Paper factory	20/20	No data	CA SCE	+ -
Yager,1986	Anatomy students	8(after)/8 (before course)	1.2 ppm	SCE	+
Suruda, 1993	Embalming course over 85 days	29(after)/29 (before course)	14.8 ppmxh (cumulative), peaks up to 6.6 ppm	MN SCE	+ -
Shaham, 1996	Pathology, anatomy	12/8	15 min personal sample range: 2.8-3.1 ppm	DPX	+(e)
Shaham, 1997	Pathology, anatomy	12/8 (for DPX) 13/20 (for SCE)	Measurements over 15 min: mean: 1.46 ppm (peaks up to 3.1)	DPX SCE	+(e) +
Shaham, 2002	Pathology	90/52	Measurements over 15 min: 0.04-5.6 ppm	SCE	+(f)
Shaham, 2003	Pathology	186/213	Same as in 2002 study	DPX	+
Ying, 1997	Anatomy students	23(after)/23 (before course)	0.508 ±0.299 mg/m³	MN	-
Ying, 1999	Anatomy students	23(after)/23 (before course)	0.508 ±0.299 mg/m³	SCE	-
He, 1998	Anatomy students	13/10	2.37 ppm (wean)	CA SCE CBMN	+ + +
Ye, 2005	FA factory	18 workers / 16 waiters / 23students (controls)	0.985±0.296 mg/m³ 0,107±0.067 mg/m³ 0.011-0.003 mg/m³	SCE	+)
Orsiere, 2006	Pathology, anatomy	59/37 18/18	TWA: 0.1 (<0.1-0.7) Peaks up to 20.4 ppm	CBMN CBMN+FISH	+*** +(d↑)
Pala 2008	Workers in different cancer research laboratories	7/25 5/15 2/17	Workers divided into low (0.005-0.026 µg/m³) and high (0.026-0.269 µg/m³) exposure groups	CBMN CA SCE	- - -
Costa, 2008(h)	Pathology	30/30	Mean 0.44, range 0.04-1.58 ppm	CBMN SCE Comet	+ + +
Jiang, 2010	Plywood industry	151/112	0.08-6,30 ppm	CBMN Comet	+ +
Jakab, 2010	Pathology (women)	37/37	Mean 0.9 (range 0.23-1.21) mg/m³	CA SCE HPRT mutat. UDS Apoptosis	+ (d↓) - - - +
Zhang, 2010	FA-resin workers	10/12	Average: 2.14 ppm, 90percentile: 4.14 ppm (g)	Aneuploidy	+
Viegas, 2010(i)	FA-resin production Pathology, anatomy	30 50 85 total controls	TWA: 0.21; peaks to 1.04 ppm TWA: 0.28; peaks up to 5.02 ppm	CBMN	- +
Ladeira, 2011(i)	Histopathology	56/85	TWA mean 0.16 (range 0.04-0.51), peaks up to 2.93 ppm	CBMN	+

Santovito, 2011	Pathology	20/16	Mean 0.0727; SE 0.0128 mg/m³	CA	+
Zeller, 2011a	Volunteers	41*	Up to 0.7 ppm; 0.4 + 4 peaks of 0.8 ppm; 4x15 min cycling at 89 W	CBMN SCE Comet Expression of FDH gene	- - - -
Costa, 2011(h)	Pathology/anatomy	48/50	Mean 0.43, range 0.04-1.58 ppm	CBMN Comet	+ +
Bouraoui, 2013	Pathology/anatomy	31/31	Between 0.2 and 3.4 ppm	CBMN with FISH	+**
Aydin, 2013	MDF production	46/46	0.10-0.33 ppm	Comet	-
Lin, 2013	Plywood industry	82 (controls) 58 38 62	0.13 mg/m³ 0.68 mg/m³ 1.48 mg/m³ (range 0.02-2.04) 0.27 mg/m³ (before / after work)	Comet CBMN DPX Comet DPX	+ (a) + (*b*) - + +
Costa, 2015 (h)	Pathology	84/87	Mean: 0.38 (range 0.08-1.39) ppm, peaks up to 3.2 ppm	Comet CA	+ (c) + (c)(d↑)

CBMN=cytokinesis-block micronucleus assay; CA=chromosomal aberrations; SCE=sister chromatid exchange; UDS=UV induced unscheduled DNA synthesis (UDS); DNA Protein Crosslinks: DPX; MN: Micronuclei without cytokinesis-block
** blood sampling before (internal control) and after last exposure*
*** significant increase only of centromere positive micronuclei (aneugenicity)*
**** increased micronuclei predominantly explained by aneugenicity*

a, b: Group comparison and trend
+ only for number of work years, not for group comparison
c: No association with time of exposure
d: Aneuploidy increased/decreased
e: Same data for DPX in Shaham et al, 1996 and 1997
f: Large overlap of participants in 2002 and 2003 study as judged by exposure data
g: Subgroup of the most highly exposed workers of a group of 43 exposed workers; aneuploidy measured in CFU-GM colonies.
h: Costa et al. (2015) comprises a group of 35 individuals already studied in the pilot study of Costa et al. (2013); therefore this latter study is not listed here; whether there also is an overlap with the study population of Costa et al. (2008) or Costa et al. (2011) cannot be ascertained, but there are obvious similarities between the groups.
i: A comparison of the control populations of Viegas et a. (2010) and Ladeira et al. (2011) indicates a substantial overlap. Whether this also relates to the pathology/anatomy groups remains unclear. Therefore these studies may not be considered completely independent.

As can be seen in Table 3, many of the older studies (<2000) only comprised small study populations (apart from Shaham et al., 2002, 2003) and positive as well as negative results were obtained. More recent investigations often report on larger groups and positive genotoxic findings predominate. The cytokinesis-block micronucleus test (CBMN) and the comet assay are the methods most frequently applied.

Towards very high doses, there seems to be a dose-dependency: For example, in the study of Costa *et al* (2008), the micronucleus frequency (given in permille) in exposed

persons (5.47 ± 0.76) was close to that in controls (3.27 ± 0.69), whereas the extremely high exposures in the study of Bouraoui *et al* (2013) resulted in figures of 25.35 ± 6.28 in exposed persons, *vs.* 7.08 ± 4.62 in controls. Another Chinese study reporting on elevated olive tail moments in the comet assay and increased micronucleus counts in peripheral lymphocytes in a plywood factory by Jiang et al (2010) fits into this frame, as the 8-hour TWA FA exposure in this study was 0.83 ppm, with individual mean exposures reaching up to 6.3 ppm. It can reasonably be assumed that FA peak exposures, which are typical for this profession, were much higher.

But an assessment of these findings predominantly has to take into consideration that after inhalation in experimental animals FA does not reach systemic circulation as confirmed by Kleinnijenhuis et al. (2013) nor does it lead to DNA adducts (Lu et al., 2010a,b, 2011, Moeller et al, 2011) or DPX, SCE or micronuclei (Speit et al., 2009) in organs distant from the site of first contact or in the blood. Therefore these findings lack biological plausibility and "were not considered by RAC (ECHA 2012) for inclusion in the discussion on classification of FA." This mechanistic argument is still valid for the interpretation of the new studies. In addition further points have to be taken into consideration:

1. The reliability of the scoring of micronuclei in the CBMN seems questionable. For instance, Ladeira et al (2011) claimed a moderately positive correlation between micronucleus frequency in peripheral blood lymphocytes and the duration of FA exposure. However, a blinded re-evaluation showed that repeated measurements of the same slide were highly variable not only between two scorers, but also when slides were evaluated by the same scorer (Speit *et al* 2012a) at different times.
2. The applicability of the CBMN to human biomonitoring has been severely challenged by Speit et al (2012a) and Speit (2013a,b) based on mechanistic grounds. While the CBMN is well suited for in vitro testing of mutagenicity, the in vivo method should be rather insensitive for the detection of mutagens/clastogens (Speit et al, 2012a). Thus the reliability of positive results obtained with the CBMN in human biomonitoring is questioned because "it is highly unlikely that DNA damage induced by exposures toward environmental and occupational chemicals in vivo leads to increased micronuclei frequencies" in the CBMN (Speit, 2013a,b).
3. Only the investigations of Orsière et al. (2006) and Bouraoui et al. (2013) differentiated by FISH staining whether the micronuclei scored were derived from clastogenicity or aneugenicity. In both studies the micronuclei predominantly contained the centromere indicating to the latter mechanism. But in vitro data of Speit et al (2011b) and Kuehner et al (2012, 2013) clearly demonstrated that FA predominantly leads to clastogenicity and not to aneugenicity. Therefore the CBMN results obtained by FISH staining again lack biological plausibility.
4. The induction of increased DNA migration as described in human biomonitoring studies also lacks plausibility. Speit et al (2007) have shown in vivo, that FA only leads to DPX (with decreased migration) and no increases have been observed down to concentrations by a factor of 10,000 below those at which crosslinking begins.
5. And finally, the relevance of positive SCE and micronuclei findings in biomonitoring studies have been questioned by Speit et al (2009) mainly because DPX present at the start of lymphocyte culture are removed during cell culture before lymphocytes start to replicate (Schmid and Speit, 2007).

In conclusion, in spite of the new publications the previous assessments of SCOEL (2008) and RAC (ECHA, 2012) are still valid. These biomonitoring studies, based primarily on mechanistic considerations, cannot be taken as proof that FA leads to systemic genotoxicity in exposed workers. This assessment is supported by the negative results obtained with human volunteers in the study of Mueller et al (2013). Under these

ED_014350_00001020-00030

conditions, Zeller et al (2011a) did not observe genotoxic effects in the CBMN, the comet assay, and the SCE test in blood samples taken after the last exposure.

7.6.1.2. Toxic effects on germ cells

The sperm count, sperm morphology and the occurrence of fluorescent bodies were investigated in 11 employees who carried out autopsies and were exposed to average FA concentrations of 0.61 to 1.32 ppm. No significant differences from the controls were found (Ward et al. 1984). The exposure levels were, however, low and the number of persons investigated small

7.6.1.3. Toxic effects on germ cells

The sperm count, sperm morphology and the occurrence of fluorescent bodies were investigated in 11 employees who carried out autopsies and were exposed to average FA concentrations of 0.61 to 1.32 ppm. No significant differences from the controls were found (Ward *et al.* 1984). The exposure levels were, however, low and the number of persons investigated small.

7.6.1.4. Local

Different mechanistic considerations apply for the interpretation of local genotoxicity because FA leads to nasal tumours in exposed rats. Speit and Schmid (2006) reviewed the results obtained with exfoliated nasal and buccal cells in exposed workers. They concluded that the published results suggest that inhalation of FA leads to increased micronuclei in nasal and buccal cells. But their review revealed that the effects were not consistent and the studies should be interpreted with caution because of lack of standardisation of the micronucleus test in these cells associated with a high assay variability. A further problem was the quality of the published studies with incomplete information and confounding factors. Therefore it was not possible to assess potential local genotoxicity in humans.

Studies published after this review are summarised in Table 4. Similar to the review of Speit and Schmid (2006), Knasmueller et al (2011) concluded that genotoxicity tests in exfoliated human nasal cells need further standardisation of applied methods and/or that sufficient information on the role of confounding factors was lacking for most protocols.

Table 4: Local genotoxicity in exposed workers and volunteers

Author	Study group	N: exp./contr.	Exp. Level	Endpoints	Result
Viegas et al, 2010	FA-resin production Pathology, anatomy	30 50 85 total controls	TWA: 0.21; peak up to 1.04 ppm TWA: 0.28; peak up to 5.02 ppm	Buccal cells	+ +
Ladeira et al, 2011	Histopathology	56/85	TWA mean 0.16 (range 0.04-0.51), peaks up to 2.93 ppm	Buccal cells	+
Speit et al, 2007a	Volunteers	21/pre-exposure values as negative control	4 h each over 10 d: 0.15 up to 0.5 ppm with 4 peaks of 1 ppm	Buccal cells	-
Zeller 2011a	Volunteers	41/pre-exposure values as	4 h each over 5 d: up to 0.7 ppm; 0.4 with 4 peaks of 0.8	Nasal cells	-

		negative control	ppm		

The studies presented and summarised in Table 4 generally comprise larger populations compared to those reviewed by Speit and Schmid (2006). While for exposed workers increased frequencies of micronuclei were observed with buccal cells, no increases were found with volunteers for nasal or buccal cells (Speit et al, 2007a; Zeller et al, 2011a). Therefore the findings in exfoliated, locally exposed cells lack consistency and the methodological critiques of Speit and Schmid (2006) and of Knasmueller et al (2011) still prevail. A consistent interpretation of local genotoxicity in exposed humans is not possible

7.6.2. Animal data

7.6.2.1. Systemic

In the rat, chromatid breaks are described in cells from lung lavage after repetitive inhalation exposures to 15 ppm after 1 and 8 weeks of exposure, but not at lower levels of exposure (Dallas et al, 1992). These findings could not be reproduced when rats were exposted up to 15 ppm over 28 days. In lung lavage cells no increase of micronuclei was found and no effect in the comet assay either directly or after gamma-irradiation to test for DNA-protein crosslink (DPX) formation (Neuss et al, 2010b). Micronuclei (MN) in the gastrointestinal epithelium were reported after gavage of FA (Migliore et al, 1989). The significance of the study is difficult to assess as only one high oral dose was given leading to local hyperaemia and haemorrhage.

Ye et al (2013) reported DPX formation in several peripheral tissues including bone marrow and peripheral blood mononuclear cells of mice exposed to FA concentrations ranging from 0.5-3.0 mg/m³ (8 h/d over 7 consecutive days). These findings are clearly in contrast to those of Yu et al (2015) (see below).

7.6.2.2. Toxic effects on germ cells

The toxic effects of FA on germ cells have been demonstrated in numerous tests with Drosophila (Alderson 1965, Herskowitz 1950, 1953), in particular after administration with the diet, and were limited to effects on early spermatocytes of the larvae (see IARC 1982). Gaseous FA had no effect. In tests for mosaic mutations in Drosophila and in the Müller-5 test for recessive lethal mutations, FA yielded positive results (Szabad et al, 1983). In a comparative test with the unstable Zeste-White assay in Drosophila melanogaster, FA produced somatic mutations, but no germ cell mutations (Rasmuson and Larsson 1992). In vitro, during the reaction of FA with adenosine, a hydroxymethyl adduct was produced. This kind of nucleoside modification is thought to have marked germ-cell-stage-specific mutagenic effects in male Drosophila larvae (Alderson 1985).

Few studies have been carried out with mammals. In a review of the dominant lethal test, FA is listed with substances for which premature death of the foetuses and pre-implantation losses were within the control range (Epstein et al, 1972). In mice (Q strain) given single intraperitoneal injections of a 35% FA solution (dose: 50 mg/kg body weight) no chromosomal changes were found in the metaphase I spermatocytes (Fontignie-Houbrechts, 1981). In the dominant lethal test, the number of pre-implantation and post-implantation losses in the first week of mating was twice the control value (Fontignie-Houbrechts, 1981). In albino rats, marked dose-dependent effects were observed in the dominant lethal test in mating weeks one to three after intraperitoneal administration of 0.125 to 0.5 mg/kg body weight (1/4 to 1/16 of the lethal dose) in the form of a 37% solution stabilized with 10% methanol. Also the fertility of the treated male rats decreased in a dose-dependent manner (Odeigah, 1997). In another test the authors found an increase in the number of abnormal sperm.

Thus, positive results were obtained in i.p. studies. This route is likely to lead to direct exposure of germ cells, bypassing the systemic circulation. This is because substances injected into the abdominal cavity can reach the testes directly via the inguinal canal. The relevance for conditions of human inhalation exposure of such results must be questioned.

FA can therefore be regarded as a potential germ cell mutagen in rodents, with mutagenic effects when it reaches the target organ and the target structures in sufficient amounts, as was demonstrated in the dominant lethal test with intraperitoneal injection of high-percentage solutions. Exposure to exogenous FA at levels which do not significantly increase the endogenous bioavailability of the substance is not expected to produce mutagenic effects on the germ cells. Specifically, this relates to exposures below the recommended OEL of 0.3 ppm. This is supported by toxicokinetic studies by inhalation in several species (see section on Toxicokinetics).

This conclusion is in line with the assessment of the US Agency for Toxic Substances and Disease Registry (ATSDR, 1999) that the results of studies in humans and experimental animals indicate that it is very unlikely that low level exposure to FA can cause developmental or reproductive damage.

7.6.2.3. Local

In vivo, DPX were detected in the epithelium of sections of the trachea (Cosma et al. 1988) and in the nasal epithelium of rats exposed to FA (Casanova and Heck 1987; Casanova et al 1989, 1994, Casanova-Schmitz and Heck 1983, Casanova-Schmitz et al. 1984, Heck and Casanova 1995, Lam et al. 1985). In monkeys, the levels of DPX were highest in the mucosa of the middle turbinates; lower concentrations were produced in the anterior lateral wall/septum and nasopharynx. Very low concentrations were found in the larynx, trachea and carina tracheae and in the proximal portions of the major bronchi (Casanova et al. 1991). The incidences of DPX varied widely in the various regions of the nasal cavity, and in the monkey in the deeper sections of the respiratory passages (Casanova et al. 1991, 1994). The distribution of DPX correlated with the probability of deposition of FA dictated by the anatomy and physiology of the various sections of the nose (Hubal et al. 1997).

In the nasal epithelium of F344 rats, DPX were still detected at FA concentrations as low as 0.3 ppm (Casanova et al. 1994). In the experiments with rhesus monkeys, they were also found at the lowest concentration of 0.7 ppm (Casanova et al 1988, 1991).

Using a physiologically based pharmacokinetic model, it was calculated that in man fewer DPX are formed in the nasal mucosa than in the rat or monkey and DPX formation was lower in the monkey than in the rat (Casanova et al. 1988, 1991; see 7.1.5).

In a long-term inhalation study with rats published by Monticello et al. (1996), point mutations were found in the p53 gene in 5 of 11 nasal tumours. The tumours expressed only the mutated gene. The role of FA in causing these mutations is unclear (Recio et al. 1992): p53 mutations have been detected in man in tumours of various genesis. In rodents, however, they are rare (Wolf et al. 1995), although the finding of p53 mutations in rat nasal SCC and the high prevalence of p53 mutations among human nasal SCC indicates that a common molecular alteration is shared between rodent and human SCC (Recio, 1997). Often the mutations are produced secondarily during the promotion or progression phase. The heterogeneous spectrum of mutations in the nasal tumours of rats suggests, thus, an important contribution of cell proliferation at such high levels.

Meng et al. (2010) determined mutation frequencies of the p53 and K-ras genes in the nasal epithelium of rats exposed to 0, 0.7, 2, 6, 10, and 15 ppm over 13 weeks. Although 2/5 untreated rats had measurable p53 mutant fractions, no dose related increases were found in treated animals. Mutation fractions were not detected for the

ED_014350_00001020-00033

K-ras gene. It was concluded that previously observed p53 mutations likely occurred after another key elements of FA-induced carcinogenesis and that FA is not carcinogenic through a mutagenic mode of action.

Speit et al. (2011a) studied the micronuclei formation in the nasal epithelium of rats exposed up to 15 ppm (6 h/d, 5 d/week, over 4 weeks). Histopathological changes and increased cell proliferation showed a dose response relationship corresponding to former studies. At the end of exposure no increase of micronuclei was found, and an increase of micronuclei was also not observed 3, 7, 14, or 28 days after a single dose of cyclophosphamide.

Recent studies differentiating between DNA adducts formed by endogenous and exogenous FA after inhalation exposure are described in the section "7.9.1. Integrating toxicokinetics and mode of action"

7.6.3. In vitro

DNA adducts, DPX, strand breaks and the induction of repair were detected in vitro. FA also produced back mutation and forward mutation in bacteria. High concentrations of FA (4 mM) produced insertions, deletions and point mutations in GC base pairs in the gpt gene of Escherichia coli (Crosby et al, 1988). Gene mutations were detected also in lymphoblasts treated with FA (Liber et al, 1989). Most of the mutations were AT —> CG transversions at specific sites. Tests with V79 cells from the Chinese hamster, on the other hand, showed that although cytotoxicity parallels sister chromatid exchange (SCE) and micronucleus (MN) formation resulting from the formation of DPX, no gene mutation occurred (Merk and Speit, 1998). Chromosomal aberrations (CA) (Natarajan et al, 1983) and SCE (Schmid et al, 1986) were reported. Thus the mutagenic effects of FA are well-documented from in vitro studies.

DPX induced by FA can be removed by repair. Half-lives of 2 to 4 hours have been reported. Accordingly, DPX can usually no longer be detected 24 hours after exposure (Cosma and Marchok, 1988; Cosma et al, 1988; Craft et al, 1987; Grafström et al., 1983, 1984; Magana-Schwenke and Moustacchi, 1980; Merk and Speit, 1998). In sections of the tracheal epithelium of rats, the DPX had been almost completely removed within 48 to 72 hours after the treatment, depending on the concentration of the instilled aqueous FA solutions (1.7-66.7 mM) (Cosma and Marchok, 1988; Cosma et al, 1988). This corresponds to a half-life of about 7 hours. Histological examination revealed hyperproliferation in the tracheal epithelium. The accumulation of DPX was investigated; because of the methods used, however, the results cannot be evaluated conclusively (Casanova et al, 1994).

Schmid and Speit (2007) studied the dose-response of genotoxicity of FA in human blood cultures in vitro. DPX were induced at FA concentrations starting from 25 µM. However, DPX induced by FA concentrations up to 100 µM were completely removed before the lymphocytes started to replicate. SCE were induced at concentrations higher than 100 µM, parallel to the induction of cytotoxicity, determined as reduction of the replication index. MN were not induced by FA concentrations up to 250 µM, the highest concentration that could be tested.

Speit et al. (2007) modelled the in vitro dose response relationship for the induction of SCE and micronuclei in V79 cells. The dose response curve showed a clear upward trend with increasing FA concentration and by regression modelling a mode-of action based threshold was indicated for both genotoxic endpoints.

In brief, there is consistent evidence for the genotoxicity of FA in in vitro systems, laboratory animals and exposed humans. DNA-protein crosslinks have been reproducibly detected in the nasal mucosa of rats and monkeys exposed to FA and provide a useful marker of genotoxicity. The biphasic behaviour of the dose-response curve for this genotoxic endpoint points to a steeper slope at 2-3 ppm in Fischer 344 rats; for rhesus Rhesus monkeys the slope is less well defined. At concentrations above 6 ppm of FA,

ED_014350_00001020-00034

genotoxicity is greatly amplified by cell proliferation, resulting in a marked increase of malignant lesions in the nasal passages (IARC, 2006).

7.6.4 Conclusions on genotoxicity

There is consistent evidence for the genotoxicity of FA in in vitro systems, laboratory animals and exposed humans. DNA-protein crosslinks have been reproducibly detected in the nasal mucosa of rats and monkeys exposed to FA and provide a useful marker of genotoxicity. The biphasic behaviour of the dose-response curve for this genotoxic endpoint points to a steeper slope at 2-3 ppm in Fischer 344 rats; for rhesus monkeys the slope is less well defined. At concentrations above 6 ppm of FA, genotoxicity is greatly amplified by cell proliferation, resulting in a marked increase of malignant lesions in the nasal passages (IARC, 2006).

7.7. Carcinogenicity

7.7.1. Human data

Over 25 cohort studies concerning professionals or industrial workers have examined the association between FA and cancer. Some have been conducted on workers exposed to FA in the chemical, garment, fibreglass, iron, woodworking, plastics and paper, pulp and plywood industries. Others are studies of professional groups (mainly health professionals, embalmers and funeral directors). Case–control studies have also been used to examine the association of FA with various cancers and, for rarer tumours such as sinonasal and nasopharyngeal cancer, they have the potential to provide greater statistical power than can normally be achieved in cohort studies. Against this advantage, however, must be set the difficulties in assessing retrospectively exposure to FA in community-based studies.

The carcinogenicity of FA has recently been re-evaluated by IARC (2006). In particular, three major cohort studies previously evaluated (IARC 1982, 1995), and since then updated for follow-up and for exposure assessment, were considered.

NCI cohort and leukaemias / lympho-haematopoietic cancers

A cohort studied by the U.S. National Cancer Institute (NCI) consisted of 25,619 workers (865 708 person-years) employed before January 1, 1966, at one of 10 U.S. industrial plants and followed through December 31, 1994. Among the cohort, there were 178 deaths from lympho-haematopoetic malignancies. Relative risks for leukaemia (69 deaths), particularly for myeloid leukaemia (30 deaths), increased with FA exposure. Compared with workers exposed to low peak levels of FA (0.1-1.9 ppm), relative risks for myeloid leukaemia were 2.43 (95% CI = 0.81 to 7.25) and 3.46 (95% CI = 1.27 to 9.43) for workers exposed to peak levels of 2.0-3.9 ppm and > or = 4.0 ppm, respectively (P(trend) =.009). Compared with workers exposed to low levels of average exposure intensity of FA (0.1-0.4 ppm), workers exposed to 0.5-0.9 ppm and > or = 1.0 ppm average intensity had relative risks of 1.15 (95% CI = 0.41 to 3.23) and 2.49 (95% CI = 1.03 to 6.03), respectively (P(trend) =.088). The relative risk for leukaemia was not associated with cumulative exposure but was weakly associated with duration of exposure (Hauptmann et al, 2003).

Marsh and Youk (2004) re-analysed the data from the updated NCI cohort (Hauptmann et al, 2003) and reproduced the results presented by Hauptmann et al (2003). Three additional analyses were performed. Exposure category-specific SMRs, based on mortality rates for the general US population, increased with increasing peak and average intensity of exposure for all leukaemias combined and for myeloid leukaemia. Findings were similar when regional mortality rates were used. The use of alternative cut-points for categories of average intensity of exposure in order to achieve similar

numbers of deaths from the combined group of all leukaemias in each exposed category resulted in similar relative risk estimates to those previously observed by Hauptmann et al (2003). Analyses of duration of time worked in the highest peak category did not generally indicate higher risks among those who had experienced high peaks for a longer time.

NCI cohort and nasopharyngeal cancers

A second publication focussed on solid cancers observed in the same cohort. In this extended follow-up of FA-exposed workers, the authors evaluated mortality from solid cancers (1,921 deaths) among 25,619 workers (865,708 person-years) employed in 10 US FA-producing or FA-using facilities through 1994. Exposure assessment included quantitative estimates of FA exposure. Standardized mortality ratios and relative risks were calculated. Compared with that for the US population, mortality from solid cancers was significantly lower than expected among subjects exposed and non-exposed to FA (standardized mortality ratios = 0.91 and 0.78, respectively). Relative risks for nasopharyngeal cancer (nine deaths) increased with average exposure intensity, cumulative exposure, highest peak exposure, and duration of exposure to FA (p-trend = 0.066, 0.025, <0.001, and 0.147, respectively). FA exposure did not appear to be associated with lung (744 deaths), pancreas (93 deaths), or brain (62 deaths) cancer. Although relative risks for prostate cancer (145 deaths) were elevated for some measures of FA exposure, the trend was inconsistent. Regarding solid cancers, some evidence was found in this cohort of FA-industry workers of an exposure-response relation with mortality from nasopharyngeal cancer (based on small numbers) but not for cancers of the pancreas, brain, lung, or prostate (Hauptmann et al, 2004).

In 2002, Marsh et al published a follow-up of their independent analysis conducted at one of the 10 plants included in the NCI cohort, the Wallingford plant or Plant 1, together with a case-control analysis (Marsh et al, 2002). They concluded that the pattern of findings suggested that the large, persistent NPC excess observed among the Wallingford workers was not associated with FA exposure, and could reflect other (non) occupational risk factors.

A re-analysis of the updated NCI cohort, concerning the mortality risks from nasopharyngeal cancer, was later presented by Marsh and Youk (2005). They pointed out that the statistically significant exposure-response relation for this malignancy in the NCI study was driven entirely by a large excess of this tumour in "Plant 1" for the highest peak exposure category (4+ ppm). An independent and larger re-analysis of Plant 1 found that this excess was not associated with FA exposure. The authors concluded that the re-analysis provided little evidence to support the suggestion of a causal association between FA exposure and mortality from nasopharyngeal cancer.

Marsh et al (2007b) conducted two additional re-analyses of the NCI cohort data which confirmed their previous conclusions (Marsh et al, 2002) that the elevated NPC risks in plant 1 were more likely due to factors external to the workplace. An additional analysis suggests that the increased risk of NPC might be associated with previous employment in the metal industry (Marsh et al, 2007a).

The second major study considered by IARC was also from the United States (NIOSH). To evaluate the mortality experience of 11,039 workers exposed to FA for three months or more in three garment plants. The mean time weighted average FA exposure at the plants in the early 1980s was 0.15 ppm but past exposures may have been substantially higher. Vital status was updated through 1998, and life table analyses were conducted. Mortality from all causes (2206 deaths, standardised mortality ratio (SMR) 0.92, 95% CI 0.88 to 0.96) and all cancers (SMR 0.89, 95% CI 0.82 to 0.97) was less than expected based on US mortality rates. A non-significant increase in mortality from myeloid leukaemia (15 deaths, SMR 1.44, 95% CI 0.80 to 2.37) was observed. Mortality from myeloid leukaemia was greatest among workers first exposed in the earliest years when exposures were presumably higher, among workers with 10 or more years of exposure,

and among workers with 20 or more years since first exposure. No nasal or nasopharyngeal cancers were observed. Mortality from trachea, bronchus, and lung cancer (147 deaths, SMR 0.98, 95% CI 0.82 to 1.15) was not increased. Mortality from leukaemia was increased almost twofold among workers with both 10 or more years of exposure and 20 years or more since first exposure (15 deaths, SMR 1.92, 95% CI 1.08 to 3.17). Mortality from myeloid leukaemia among this group of workers appeared also significantly increased (8 deaths, SMR 2.55, 95% CI 1.10 to 5.03). It was concluded that the results supported a possible relation between FA exposure and myeloid leukaemia mortality. Limitations of the study include limited power to detect an excess for rare cancers such as nasal and nasopharyngeal cancers and lack of individual exposure estimates (Pinkerton et al, 2004).

The third major study considered by IARC had been conducted in the U.K. This study extended by 11 years the follow-up of an existing cohort of 14,014 men employed after 1937 at six British factories where FA was produced or used. Subjects had been identified from employment records, and their jobs had been classified for potential exposure to FA. Standardized mortality ratios (SMRs) were derived using the person-years method and were compared with the expected numbers of deaths for the national population. During follow-up through December 31, 2000, 5185 deaths were recorded, including two from sino-nasal cancer (2.3 expected) and one from nasopharyngeal cancer (2.0 expected). Relative to the national population, mortality from lung cancer was increased among those who worked with FA, particularly in men in the highest of four estimated exposure categories (>2 ppm) (SMR = 1.58, 95% confidence interval = 1.40 to 1.78), and the increase persisted after adjustment for local geographic variations in mortality (SMR = 1.28, 95% confidence interval = 1.13 to 1.44). However, there was a statistically non-significant decrease in the risk of death from lung cancer with duration of high exposure (P(trend) =.18), and this risk showed no trend with time since first high exposure (P(trend) =.99) (Coggon et al, 2003).

The IARC (2006) Working Group concluded that there was sufficient evidence in humans that FA causes nasopharyngeal cancer, on the grounds that there was a statistically significant excess of deaths from nasopharyngeal cancer in the largest and most informative cohort study of industrial workers (Hauptmann et al., 2004), with statistically significant exposure-response relationships for peak and cumulative exposure. These conclusions were proposed to be re-evaluated (SCOEL, 2008) in light of the studies conducted by Marsh and colleagues (Marsh et al., 2002; Marsh and Youk, 2005; Marsh et al. 2007a,b). An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest US cohort of embalmers (Hayes et al., 1990), and an excess of cases of nasopharyngeal cancer was observed in a Danish study of proportionate cancer incidence among workers at companies that manufactured or used FA (Hansen and Olsen, 1995). Although other cohort studies reported fewer cases of nasopharyngeal cancer than expected (Walrath and Fraumeni, 1983; Coggon et al., 2003; Pinkerton et al., 2004), the Working Group noted that the deficits were small and the studies had low power to detect an effect on nasopharyngeal cancer. Of seven case-control studies of nasopharyngeal cancer (Olsen et al, 1984; Vaughan et al, 1986a,b; Roush et al, 1987; West et al, 1993; Armstrong et al, 2000; Vaughan et al, 2000; Hildesheim et al, 2001), five found elevations of risk for exposure to FA.

It was mentioned that leukaemia mortality, primarily myeloid-type, was increased in six of seven cohorts of embalmers, funeral-parlour workers, pathologists, and anatomists. These findings had previously been discounted by IARC because an increased incidence of leukaemia had not been seen in industrial workers. The recent updates, however, reported a greater incidence of leukaemia in two cohorts of US industrial workers and US garment workers, but not in a third cohort of United Kingdom chemical workers. A recent meta-analysis found that, overall, the relative risk for leukaemia was increased and did not vary significantly among studies (Collins and Lineker, 2004). Several case-control studies had associated exposure to FA with sinonasal adenocarcinoma and squamous-cell carcinoma. However, confounding from wood dust exposure occurred in these studies, and no excess of sinonasal cancer was reported in the updated cohort studies. The IARC

ED_014350_00001020-00037

Working Group concluded that there was limited evidence in humans that FA causes sinonasal cancer (IARC, 2006).

Several case-control studies associating exposure to FA with sino-nasal adenocarcinoma (possibly confounded by wood dust) and squamous-cell carcinoma were key for the conclusion of IARC that FA could cause nasopharyngeal cancer in humans (IARC, 2006). In addition, IARC reconfirmed that there is sufficient evidence that FA can cause nasopharyngeal cancer and additionally that there was sufficient evidence that FA can cause leukaemia, but limited evidence that FA can cause sinonasal cancer in humans (IARC, 2012).

A recent joint EU evaluation of cancer hazard has been performed by RAC (ECHA, 2012). By long-term inhalation in rats and mice, nasal SCC and benign tumours (papillomas and adenomas) were the key effects. Also, RAC evaluated the epidemiological studies, including their strengths and weaknesses, and found the key effect to be nasopharyngeal cancer. Based on the overall consistency within and between species, and biological plausibility (comprising genotoxic effect of FA), RAC concluded that there is "limited evidence of carcinogenicity in humans (Car. 1B)"; the human evidence was from nasopharyngeal cancer. RAC concluded further that "no evidence of induction of tumours at distant sites and in particular in the lympho-haematopoietic system was obtained by inhalation".

A somewhat different conclusion was reached by NRC (2014), which found that there was a clear and convincing epidemiological evidence of a causal relationship between FA exposure and occurrence of nasopharyngeal and sinonasal cancer, and myeloid leukaemia; carcinogenic effect at any additional sites does not meet the requirement of limited evidence. Sufficient evidence was accepted if at least two strong or moderately strong studies with different study design and populations showed an association between FA exposure and a specific cancer type and for which chance, bias and confounding could reasonably be ruled out. An epidemiological study was considered strong if it comprised a large population with long duration of exposure and sufficient follow-up for latency, had an appreciable FA gradient, and the FA exposure being well characterized. Acceptance of a systemic carcinogenic effect does not require that the mechanism is known or FA being systemically available. Also, the presence of negative finding did not necessarily negate positive findings. It is noted that limitations of the key studies were not addressed. The different conclusions are due to differences in evaluation procedures. All recent studies considered strong by NRC (Beane Freeman et al, 2009, 2013; Hauptmann et al, 2009; Meyers et al, 2013) are considered below.

For recent discussions, the further epidemiological studies of human FA exposure and lympho-haematopoietic and nasopharyngeal cancers have been pivotal. One (Beane Freeman et al., 2009, 2013) was an update of mortality in a retrospective NCI cohort of industrial workers as shown in Table 5, and the study of Hauptmann et al. (2009) was a proportional mortality and case-control study among embalmers. Both studies included subjects with considerable exposure to FA and both were focussed on myeloid leukaemias. There is also an update of the US NIOSH garment industry cohort mortality study (Meyers et al, 2013) and British cohort from six factories (Coggon et al, 2014). Also, a Finnish (Siew et al, 2012) and an Italian cohort (Pira et al, 2014) have been studied.

ED_014350_00001020-00038

Table 5. *Exposure-dependent effect of FA on development of nasopharyngeal cancer in the three formaldehyde exposure metrics in the US National Cancer Institute Cancer Cohort.*

The reference group was the lowest exposure category in each exposure metric (Beane Freeman et al., 2013). The cohort comprises 25,619 workers. Numbers of NPC cases are indicated by N and a significant increase is indicated in ***bold****.*

Peak exposure		Average intensity		Cumulative exposure	
ppm	RR (95%CI) (N)	ppm	RR (95%CI) (N)	ppm x year	RR (95%CI) (N)
0	4.4 (0.3-54) (2)	0	6.8 (0.5-84) (2)	0	1.9 (0.3-12) (2)
>0 - <2.0	RR=1 (1) Reference	0.1-0.4	RR=1 (1) Reference	>0-<1.5	RR=1 (4) Reference
2. 0- <4.0	NA[a)] (0) Apparent NOAEL	0.5-0.9	2.4 (0.15-39) (1) Apparent NOAEL	1.5-<5.5	0.86 (0.1-7.7) (1) Apparent NOAEL
≥ 4.0	7.7 (0.9-62) (7)	≥1	**12 (1.4-97) (6)**	≥5.5	2.9 (0.6-13) (3)
P (trend FA groups)=0.005 P (trend FA groups + controls)=0.10		P (trend FA groups)=0.09 P (trend FA groups + controls)=0.16		P (trend FA groups)=0.06 P (trend FA groups + controls)=0.07	

a) Not applicable (NA).

In the NCI FA cohort, previously followed through 31 December 1979 and updated through 31 December 1994, FA exposure was found associated with an increased risk for leukaemia, particularly myeloid leukaemia, which increased with peak and average intensity of exposure (see SCOEL 2008). Beane Freeman et al (2009) extended the follow-up through 31 December 2004 (median follow-up = 42 years), for 25 619 workers employed at one of 10 FA-using or FA-producing plants before 1966. When follow-up ended in 2004, there were statistically significant increased risks for the highest vs. lowest peak FA exposure category ≥ 4 ppm vs. > 0 to < 2.0 ppm) and all lympho-haematopoietic malignancies [relative risk (RR) = 1.37; 95 % confidence interval (CI) = 1.03–1.81, P trend = 0.02] and Hodgkin's lymphoma (RR = 3.96; 95 % CI = 1.31–12.02, P trend = 0.01). Statistically non-significant associations were observed for multiple myeloma (RR = 2.04; 95 % CI = 1.01–4.12, P trend > 0.50), all leukaemia (RR = 1.42; 95 % CI 0.92–2.18, P trend = 0.12) and myeloid leukaemia (RR = 1.78; 95 % CI = 0.87–3.64, P trend = 0.13). There was little evidence of an association for lympho-haematopoietic malignancy with average intensity or cumulative exposure at the end of follow-up in 2004. However, disease associations varied over time. For peak exposure, the highest FA-related risks for myeloid leukaemia occurred before 1980, but trend tests attained statistical significance in 1990 only. After the mid-1990s, the FA-related risk of myeloid leukaemia declined (Beane Freeman et al, 2009).

Beane Freeman et al (2013) further extended the follow-up of the NCI cohort of workers in FA industries (n = 25 619) through 2004. During 998 239 person-years, 13 951 deaths occurred. With one additional death, albeit occurring in the lowest exposure category, previously observed excesses for nasopharyngeal cancer (n = 10) persisted for peak, average intensity and cumulative exposure; RRs in the highest exposure categories were 7.66 (95 % CI: 0.94–62.34), P-trend = 0.005, 11.54 (95 % CI: 1.38–96.81), P-trend = 0.09, and 2.94 (95 % CI: 0.65–13.28), P-trend = 0.06, respectively. For all cancer, solid tumours and lung cancer, standardised mortality ratios (SMRs) among exposed workers were reported to be elevated, but internal analyses, as described by the

authors, revealed no positive associations with FA exposure. Subsequent to this publication, criticism was raised regarding the data in the NCI cohort study (Marsh *et al* 2014), which included limitations of the statistical methods (instability of the reference group where only one nasopharyngeal cancer case was present, limitations in the trend test, and not adequately having addressed heterogeneity between plants), using non-significant results in interpretations and lack of consistency with other major cohorts. The limitation of the previous update is also relevant for the new update. Six of 10 previously observed nasopharyngeal cancers were observed in one, the Wallingford plant, whereas a decreased risk of nasopharyngeal cancer was observed in the other nine plants. Many of the cases from the Wallingford plant had a short and low average intensity of FA exposure, and the cancers may have been due to external employment in the ferrous and non-ferrous metal industries (Marsh et al. 2007a). Also, there is a lack of consistency across studies, as no excess of nasopharyngeal cancer was observed in other comprehensive studies (Coggon et al, 2014; Hauptmann et al, 2009; Meyers et al, 2013; Pira et al, 2014; Siew et al, 2012).

Recently, a follow-up has been conducted on the US NIOSH garment industry cohort (Meyers et al, 2013), which is one of the three largest prospective cohorts. The study comprised 11 043 workers. Causes of death were obtained from 99.7 % (3 904) of the identified deaths. About 77 % had year of first exposure in 1970 or earlier. In the early 1980s, personal FA sampling was performed among 549 employees. The geometric mean FA concentration was 0.15 ppm with a geometric standard deviation of 1.90. No exposure data was available before this time, but FA concentrations were believed to have decreased over time. SMRs (and 95 % CIs) were calculated and, in addition, internal comparisons were made using directly standardised rate ratios (SRRs and 95 % CIs) for "duration of exposure".

The SMRs were similar to that of the US population for all cancers, for lympho-haematopoietic cancers (leukaemias, Hodgkin disease, non-Hodgkin lymphoma, and multiple myeloma), for buccal cavity and pharyngeal cancers, for respiratory cancers, and for brain cancer and other parts of the nervous system. Stratifying SMRs for "year of first exposure" (< 1963, 1963–1970, ≥ 1971) neither showed significant associations for lympho-haematopoietic cancers, for trachea, bronchus and lung cancer, and for brain cancer and other parts of the nervous system, nor was this the case with SMRs for "time since first exposure (< 10, 10–19, ≥ 20 years). Associations between "duration of FA exposures" (< 3, 3–9, ≥ 10 years) and risks of cancer were studied with SMRs and SRRs. There was no exposure-dependent increase in risks for lympho-haematopoietic cancers and non-Hodgkin lymphoma. The risks increased with the length of the exposures for leukaemia, myeloid leukaemia and acute myeloid leukaemia, but were not statistically significant. For multiple myeloma, the SMRs for the exposure groups were 1.16 (0.50–2.29), 2.03 (1.01–3.64) and 0.64 (0.17–1.64), respectively, and the SRRs were 1.00 (reference), 1.22 (0.46–3.26) and 0.28 (0.08–099), respectively. For trachea, bronchus and lung cancer, the SMRs were 1.23 (1.02–1.46), 1.14 (0.91–1.41) and 0.71 (0.53–0.91), respectively, and the SRRs 1.00 (reference), 1.00 (0.75–1.33) and 0.74 (0.48–1.13), respectively. Thus, where the values were statistically significant, they were not associated with the length of exposure. Nevertheless, among persons with ≥ 10 years of exposure and ≥ 20 years since first exposures, the risk for leukaemia (23 deaths, SMR: 1.74 (1.10–2.60)) was significantly increased when multiple causes of death were considered.

Additionally, the association between duration of exposure and leukaemia (36 cases) and myeloid leukaemia (21 cases) was studied using four multivariate Poisson regression models (adjusted for age, year of birth and years since first exposure), where exposures were either untransformed or transformed (log, square root, and categorical (< 1.6 (reference), 1.6– < 6.5, 6.5– < 16, 16– < 19 and ≥ 19 years)). Only the untransformed model for leukaemia and the categorical model for myeloid leukaemia were statistically significant. Nevertheless, for leukaemia and myeloid leukaemia, the rate ratio was significantly increased in the fourth category (4.56 (1.30–16.2) and 6.42 (1.40–32.2), respectively), but not for the other (2th, 3th and 5th) categories.

The SMR for chronic obstructive disease was increased (1.16, CI: 1.00–1.34), as was the SMR (1.46; 1.08–1.93) for the year of first exposure in the period 1963–1970), the SMR (1.16; 1.00–1.35) for ≥ 20 year for time since first exposure, and the SMRs for duration of exposure (< 3, 3–9 and ≥ 10 years), which were 1.44 (1.13–1.80), 1.16 (0.87–1.51) and 0.94 (0.72–1.21), respectively.

The authors concluded that the study showed limited evidence of an association between FA exposure and leukaemia, but little evidence for an increased risk of mortality from buccal cavity, pharyngeal (including nasopharyngeal), respiratory and brain cancer, and for Hodgkin disease. Limitations of the study are lack of quantitative FA exposures and lack of ability to take smoking into account.

A meta-analysis of Schwilk et al. (2010) focussed on high-exposure groups and myeloid leukaemia. The analysis included two large studies in particular: one involving > 25 000 workers in US FA industries and the other involving a cohort of > 13 000 funeral directors and embalmers. FA was found associated with increased risks of leukaemia (RR = 1.53; 95 % CI = 1.11–2.21; p = 0.005; 14 studies), specifically myeloid leukaemia (RR = 2.47; 95 % CI = 1.42–4.27; p = 0.001; 4 studies). This study was interpreted by the authors to provide evidence of an increased myeloid leukaemia risk with high exposures to FA. However, the analysis has been criticised to suffer from methodological shortcomings. The study did not use all available information. The chosen highest exposure cut points varied across the combined studies, which introduced heterogeneity; the homogeneity tests used in the study were considered insensitive. Predictive intervals are recommended instead of confidence intervals and the findings of elevated leukaemia and myeloid leukaemia risks were far from significant if using these techniques in the data analyses (Morfeld, 2013).

Hauptmann et al (2009) investigated the relation of mortality to work practices and FA exposure levels among American embalmers in a case-control study. Professionals employed in the American funeral industry who died between 1 January 1960 and 1 January 1986 from lympho-haematopoietic malignancies (n = 168), brain tumours (n = 48) or nasopharyngeal cancers (n=4) were compared with deceased matched controls (n = 265) with regard to lifetime work practice. Exposures in the funeral industry were obtained by interviews with next of kin and co-workers, and predictive models to estimated levels of FA exposure. Mean peak concentrations were 8.1-10.5 ppm (model predicted as the maximum 15-minute average intensity ever experienced over all embalmings over all years) and average FA intensity 1.5-1.8 ppm while embalming. Cases were exposed for about 32 years. With one myeloid leukaemia in the reference group, odds ratio (OR (95% CI)) for myeloid leukaemia was 11.2 (1.3-95.5) in the ever embalming versus the never embalming group. Mortality from myeloid leukaemia increased statistically significantly only with increasing number of years of embalming (P for trend = 0.020) and with increasing peak FA exposure (P for trend = 0.036). There was no significant trend in any of the exposed group (duration of years with embalming, number of embalmings, cumulative FA exposure, average FA exposure while embalming, 8-hour TWA FA intensity and peak FA exposure) within the exposed groups themselves (P for trend=0.58-0.98). Odds ratios (ORs) were roughly about 10 (range: 5 to 15) in exposed groups. To increase stability of the risk estimates, subjects who performed fewer than 500 lifetime embalmings were used as the reference group. The OR in this analysis was roughly about 3 (range: 0.5-3.9) in the "exposed" groups. No true trend tests are available for this evaluation as the authors without explanation adhered the results of the trend tests from the first (unstable) analysis to this (more stable) analysis. However, ORs for myeloid leukaemia were significantly increased for duration of years with embalming at >20-34 years and >34 years, which was 3.2 (1.0-10.1) and 3.9 (1.2-12.5), respectively, with the highest number of embalmings (>3068), 3.0 (1.0-9.2), and at the highest cumulative FA exposure (ppm x hours: > 9253), 3.1 (1.0-9.6). Exposures were not related to lymphohaematopoietic malignancies of the lymphoid organs (non-Hodgkin lymphoma, multiple myeloma, all lymphoma and Hodgkin disease) or to monocytic leukaemia, polycythaemia vera or myelofibrosis, brain cancer or nasopharyngeal cancer (0.1 (0.01-1.2)). It was concluded by the authors that duration of

embalming and related FA exposures in the funeral industry were associated with statistically significantly increased risk for mortality from myeloid leukaemia.

In response to this study, Cole et al (2010) indicated that a significant excess of mortality from any form of lympho-haematopoietic cancer was not reported, and challenged the interpretation of the authors. Checkoway et al. (2012) reviewed and summarised the total published epidemiological literature in the PubMed database of the National Library of Medicine during 1966–2012. The literature was categorised according to study design and population: industrial cohort studies, professional cohort studies and population-based case-control studies. It was found that findings from occupational cohort and population-based case-control studies were very inconsistent for lympho-haematopoietic malignancies, including myeloid leukaemia. Apart from some isolated exceptions, relative risks were close to one, and there was little evidence for dose-response relations for any of the lympho-haematopoietic malignancies. It was concluded that at present, there is no consistent or strong epidemiologic evidence that FA is causally related to any lympho-haematopoietic malignancy. The absence of established toxicological mechanisms was found to further weaken the arguments for causation. This view was seconded by a meta-analysis of epidemiological data on FA exposure and risk of leukaemia and risk of nasopharyngeal cancer by Bachand et al (2010). Moreover, a critical review and data re-analysis by Gentry et al (2013), in combination with toxicological and mechanistic studies, did not support a mechanism for a causal association between formaldehyde exposure and myeloid or lymphoid malignancies.

Airway cancers associated with FA exposures were studied in a Finnish cohort with 1.2 million employees. All men born between 1906 and 1945, and employed during 1970 were included. The follow-up was in the Finnish Cancer Register for nasal cancer (292 cases), cancer of the nasopharynx (149 cases) and lung cancer (30 137 cases) during the period 1971–1995. The Finnish job-exposure matrix was used to estimate exposures. Duration of exposure was estimated from census data. A latency period of 20 years was accepted. Number of exposed cases (N), relative risk (RR) obtained by comparison with unexposed, and 95 percent confidence intervals were estimated (N; RR (95 % CI)). The risks of nasal cancers (17; 1.1 (0.6–1.9), nasal squamous cell carcinoma (9; 1.0 (0.4–2.0)) and nasopharyngeal cancer (5; 0.9 (0.3–2.2)) were not increased. The risk was slightly increased for lung cancer (1 831; 1.2 (1.1–1.3)). However, the risk in the highest exposure group (≥ 1 ppm) was not increased. Thus, the authors considered the increased risk to be due to residual confounding effects of smoking and co-exposures, including asbestos and crystalline silica. FA exposures were below 1 ppm in most occupations. Only flour layers, and varnishers and lacquers had average exposures at 1 ppm (Siew et al 2012). Overall, this study found no increase in portal-of-entry cancer at low FA concentrations in occupational settings.

A follow-up through December 2012 was conducted in the British (UK) cohort from six factories (see SCOEL/SUM/125) comprising 14 008 men in the period 1941–2012 (Coggon et al 2014). In the period, 7 378 men had died. 3,991 were at some time highly exposed. In the whole population, the standardised mortality ratio [SMRs (95 % CI)] for all cancers [1.10 (1.06–1.15)], stomach [1.29 (1.11–1.49)], rectum [1.23 (1.01–1.49)], and for lung cancer [1.26 (1.17–1.35)] was significantly increased based on the national death rate for England and Wales. Prostate cancer was significantly decreased [0.80 (0.68–0.94)]. No significant increase was seen for cancer on the lips, tongue, mouth, oesophagus, large intestine, liver, pancreas, bladder, kidneys, brain and nervous system, pharynx, nose and nasal sinuses, larynx and for the different hematopoietic malignancies. The cohort was stratified for levels of exposure, where the exposure was >2 ppm in the high exposure group. Significantly increased SMR in the high exposure group was observed for all cancers [1.28 (1.20-1.37)], cancer in the oesophagus [1.45 (1.03–1.98), stomach (1.51 (1.18–1.90)], lungs [1.59 (1.42–1.77)] and the lips [9.98 (1.21–36.04); observed/expected: 2/0.2]. No increase was seen for non-Hodgkin lymphoma [0.90 (0.48–1.55)], multiple myeloma [1.18 (0.57–2.18)], leukaemia [0.82 (0.44–1.41)] and myeloid leukaemia 0.93 [0.40–1.82)]. Exposure in the high exposure group was further stratified for duration of exposure (<1 year, 1–14 years and

≥ 15 years). For oesophagus and lung cancer, the SMR was highest in the group with the shortest exposure (< 1 year), and for stomach and rectum cancer the SMRs were largely independent of the length of the exposure period. Additionally, the authors included a nested case-control analysis of cancer in the upper airways, larynx, mouth, pharynx, tongue, and for all leukaemia and myeloid leukaemia. ORs for these cancers were independent of the duration of the exposure. The authors ascribed the increases in risk estimates to non-occupational confounding factors, which may include smoking and socioeconomic factors and concluded that the study provided no evidence that FA posed an increased hazard either of upper airway cancer or of myeloid leukaemia. It was noted that the study was not able to take smoking and socioeconomic factors into account.

Also, an Italian cohort with subjects employed in a factory producing laminate plastic, decorative papers and craft papers, using phenolic and melamine resins, has been established (Pira et al, 2014). The major risk was considered to be FA exposure, but FA concentrations were not reported. The cohort comprised 2750 employees from the period 1947 to 31 May 2011, who have been employed at least 180 days. Data on survival (80.3%), death (16.6%, N=457) and emigration (3.1%) were collected. Cause of death could not be retrieved for 26 out of 457 (5.7%) deceased employees. Person-years of observation were 70,933 in the analysis. Expected number of death (E) and SMRs were obtained by comparison with the regional deaths rates. Observed deaths (O) and SMR (O, SMR (95%CI)) for lymphoma (4; 0.74 (0.20-1.90), myeloma (O/E=0/2.3), leukaemia (5; 0.92 (0.30-2.15) and for all lympho-haematopoietic neoplasms (9; 0.69 (0.31-1.30) were not increased. Neither was an increased risk of cancer observed for all cancers (149; 0.80 (0.68-0.94). The risk was non-significantly increased for oral and pharynx cancer (9; 1.49 (0.68-2.82) and for bladder cancer (10; 1.51 (0.72-2.77)). For oesophagus, stomach, colorectal, liver, pancreas, larynx, lung, breast, prostate, kidney, and brain and CNS cancer, the SMRs were below one. The study has a long follow-up period, but a limitation is the lack of quantitative FA exposures.

7.7.2. Animal data

In a 2-year inhalation study with F344 rats, squamous cell carcinomas of the nose were observed. Exposure was to FA concentrations of 0, 2.0, 5.6 and 14.3 ppm, for 6 hours/day on 5 days/week. All the animals exposed to FA developed rhinitis, epithelial dysplasia and metaplasia in the nasal cavity. After 18 months, 15/40 animals of the high exposure group had developed hyperplasia. In all the groups exposed to FA, metaplasia preceded dysplasia. If the exposure was interrupted for longer than 3 months, the rhinitis and metaplasia began to regress. After 24 months, squamous cell carcinomas were found in the nasal cavities only in the middle dose group (0.9 %) and in the high dose group (44 %). In the high dose group, undifferentiated carcinomas and sarcomas were also found. Also the number of polypoid adenomas was slightly increased in the male animals. The total tumour incidence in the high dose group was 48.7 % (Kerns et al. 1983, Swenberg et al. 1980). The formation of nasal tumours in the rat after high level exposure to FA (> 6 ppm) has been confirmed in other studies (Feron et al., 1988; Monticello et al, 1996; Woutersen et al, 1989).

In another long-term study over 28 months, F344 rats were exposed to FA concentrations of 0, 0.3, 2.0 and 15 ppm for 6 hours/day, 5 days/week. Although keratinizing squamous cell carcinomas were found only in the high dose group (in 13 of 32 animals), the incidence of epithelial hyperplasia and metaplasia of the nasal respiratory mucosa was significantly increased in all exposed groups. As inflammatory infiltration of the nasal mucosa, erosion and oedema were described in both the controls and the exposed animals, the possibility cannot be excluded that the hyperplasia and metaplasia were caused by the interaction of FA and inflammatory damage to the nasal mucosa (Kamata et al, 1997). Therefore, this study cannot be included in the present assessment. Gelbke et al (2014) analysed this study in detail and found important deficiencies in reporting of the histopathological findings. Putting this study into context with the whole database available including the most recent investigations, they arrived

at the conclusion that that a NOAEC for histopathological lesions in the upper respiratory tract of experimental animals can be defined at 1 ppm.

In a 2-year inhalation study with B6C3F1 mice exposed to FA concentrations of 0, 2.0, 5.6 or 14.3 ppm for 6 hours/day on 5 days/week, squamous cell carcinomas of the nasal cavity were found in only 2/240 animals (0.8 %) of the high dose group. Epithelial metaplasia and dysplasia of the respiratory epithelium were, however, also observed (Kerns et al., 1983).

In hamsters exposed to concentrations of 10 or 30 ppm, no tumours were found (Dalbey, 1982; IARC, 1995; WHO, 1989) and the incidence of non-neoplastic changes of the nasal epithelium was low.

FA was administered in the drinking water for 2 years to Wistar rats in doses of 0, 10, 50 or 300 mg/kg body weight and day (Tobe et al., 1989) and 0, 1.2, 15 or 82 mg/kg body weight and day for male animals and 0, 1.8, 21 or 109 mg/kg body weight and day for female animals (Til et al., 1989). No changes were produced with doses up to 10 mg/kg body weight and day, and 15 and 21 mg/kg body weight and day, respectively. In almost all animals given doses from 50 mg/kg body weight, and 82 and 109 mg/kg body weight, histopathological changes in the forestomach (hyperplasia, keratinisation) and inflammation and ulcers of the glandular stomach were found. In addition, at doses of 82 and 109 mg/kg body weight per day, food and liquid consumption, and body weight gains were reduced. There was no increase in the incidence of tumours (Tobe et al., 1989; Til et al., 1989). Til and associates note, however, that some of the histopathological changes they classified as hyperplasia could have been classified as papillomas by other pathologists. In the study of Til et al. (1989), also renal changes (increased relative kidney weights, necrosis), and changes in the composition of the urine were observed in the female animals of the high dose group; the authors attribute this to the reduced drinking-water consumption.

In another drinking-water study, FA was administered to 7-week-old male and female Sprague-Dawley rats for 104 weeks in concentrations of 0, 10, 50, 100, 500, 1000 or 1500 mg/l drinking-water. In addition, 25-week-old male and pregnant female animals, and later their offspring were given FA in concentrations of 0 or 2500 mg/l. Reduced body weights were found only in the animals (offspring) exposed from the embryonal phase. In the animals of the groups exposed to FA concentrations of 50 mg/l and above and the animals of the 2500 mg/l group, the incidence of leukaemia (lymphoblastic leukaemia, lymphosarcomas) was increased in a dose-dependent manner (controls 3.5%, 10 mg/l: 3.0%, 50 mg/l: 9%, 500 mg/l: 12%, 1000 mg/l: 13%, 1500 mg/l: 18%, 2500 mg/l: 11.1 %). Data for the statistical significance of the findings or for the historical controls were not given by the authors (Soffritti et al., 1989). Despite criticism of this study, IARC (1995) regarded these data as being dose-dependent and significantly different from the data for the controls. Benign and malignant gastrointestinal tumours, which according to Sofritti et al. are very rare in this strain of rat (all incidences < 0. l%), were increased in particular in the animals of the following groups: 1000 mg/l (l%: leiomyosarcomas), 1500 mg/l (2%: adenomas) and 2500 mg/l (parent animals: 2.8%: papillomas and acanthomas, 2.8%: adenocarcinomas; offspring: 1.4%: adenomas, 1.4%: squamous cell carcinomas, 1.4%: adenocarcinomas, 2.7%: leiomyosarcomas) (Soffritti et al. 1989). The validity of this study has been questioned as a result of its conduct and the methods used (Feron et al., 1990).

Soffritti et al. (1989, 2002) reported about a 104 week study in male and female Sprague-Dawley rats exposed to 10, 50, 100, 500, 1000, 1500 and 2500 mg/l FA in drinking water. Animals were kept until spontaneous death. An increase of malignant tumours at various sites was noted, in particular of gastro-intestinal tumours and leukaemias. The study is difficult to evaluate because it was not conducted according to GLP standards and documentation has not been sufficient. Several deficiencies were noted by IARC (2006), among others the unexplained substantial increase for the total

ED_014350_00001020-00044

number of animals with haemo-lymphoreticular neoplasms reported after the extensive histopathological examinations in 1989 and 2002.

With repeated exposures from 6 to 22 hours per day in rats and monkeys, the histopathologic NOAEC was 1 ppm for damage of the nasal epithelium. This suggested that the FA concentration may be more important for cytotoxicity than the total FA dose. In rats, FA caused nasal squamous cell carcinoma (SCC), which is the critical cancer type in rats. Fischer 344 and Sprague-Dawley rats were more sensitive in developing SCC than Wistar rats, mice and hamster. Results from four long-term studies with the sensitive rat strains showed an apparent NOAEC for SCC at 2 ppm and an apparent LOAEC at 6 ppm (Nielsen and Wolkoff 2010; Nielsen at al., 2013). In rats, epithelial cell damage-induced cell proliferation was shown experimentally to be a key mechanism for development of SCC; in Wistar rats, no SCC could be induced at ≤ 1 ppm FA even with induced cell proliferation (Woutersen et al., 1989). In addition to SCC in rat nose, FA exposure could also induce a lower number of (benign) polypoid adenomas at high FA levels. This type of lesion is unlikely to be pre-stage of the (malignant) SCC (Gelbke et al 2014) and thus not considered a key effect.

In rats and mice, long-term inhalation of FA has not shown convincing development of lymphohematopoetic malignancies (WHO, 2010; Nielsen and Wolkoff, 2010; Golden, 2011; Rhomberg et al., 2011). Nevertheless, if such an effect had been masked by a high mortality in rats (IARC, 2012) and mice (WHO, 2010; IARC, 2012) due to development of nasal SCC at the high exposure levels, the incidence would be much lower than for SCC in rats, which therefore is considered the more sensitive endpoint (WHO, 2010).

7.8. Reproductive toxicity

As FA has been shown not to reach tissues far of the site of first contact, i.e. the upper respiratory tract after inhalation, data concerning these endpoints will not be reviewed here in detail. For a documentation of available studies reference can be made to a recent review of Nielsen et al. (2013).

The lack of the effects was supported by a review and meta-analysis (Collins et al. 2001). This review concluded that there was no convincing evidence of reproductive or developmental toxicity in animal studies at FA exposures by routes, which were relevant for risk assessment of workplace exposure levels.

7.9. Mode of action and adverse outcome pathway considerations

Experimental findings:

Experimentally, FA elicits local tumours in the upper respiratory tract. It appears plausible that the occurrence of tumours in the nasal mucosa of rats and mice is the result of chronic proliferative processes caused by the cytotoxic effects of the substance. Evaluation of the data for the carcinogenic effects confirms this assumption. The dose-response relationships for all the parameters investigated, such as damage to the nasal epithelium, cell proliferation, tumour incidence, the formation of DNA-protein-crosslinks (DPX) and DNA-adducts, is very flat for low level exposures and becomes much steeper at higher levels of exposure. For all the parameters mentioned, with the exception of the formation of DPX and DNA-adducts, concentrations, which did not produce effects, were demonstrated in the respective studies. The possibility of the formation of DPX or DNA-adducts cannot be excluded even with low levels of exposure. FA-induced DPX are rapidly repaired, as evidenced in a number of biological systems (see Genotoxicity section) but

they may also be a source of DNA adducts being caused by endogenous (dG- and dA-adducts) or exogenous FA (dG-adducts). In addition, the physiological proliferation rate in the respiratory epithelium is low, and as long as this is not increased (which requires exposure to concentrations of more than 2 ppm), the probability that DPX are transformed into mutations is low. In the low dose range, which does not lead to an increase in cell proliferation, it has therefore been considered that the observed experimental genotoxicity of FA plays no or at most a minor part in its carcinogenic potential so that no significant contribution to human cancer risk is expected (Bolt, 1987; DFG, 2000; Conolly et al., 2004). Such a conclusion is supported by dosimetry models (Kimbell et al., 2001a,b) and by results of a numerical risk assessment which, for persons exposed to concentrations of 0.3 ppm at the workplace for 40 years, yielded a very low additional cancer risk for non-smokers of 1.3×10^{-8} and for smokers of 3.8×10^{-7} (CIIT, 1999).

Conolly et al. (2004) estimated human respiratory tract cancer risk based on 1) the use of computational fluid dynamics to model local impact of FA, 2) the association of the local impact with DPX formation and cyto-lethality leading to regenerative cell proliferation, and 3) a two-stage clonal growth model to link DPX and cell proliferation with tumour formation. The model incorporated a hockey stick shaped and a J-shaped dose response relationship for cell proliferation, the latter because this was indicated by the data available at that time. Maximum likelihood estimates of additional risks were calculated for different exposure levels and physical workloads. As in the study of Andersen et al. (2010) no clear indication for a J-shaped dose response was obtained, only risks based on the hockey shape will be given here. For example, for a non-smoking worker with "light work" occupational exposure (80 year lifetime with an environmental exposure of 4 ppb and 40 years of work at 0.3 ppm, 8 h/d, 5 d/week) the additional risk was 1.79×10^{-7} and for a smoker 4.14×10^{-6}. The additional risks related to lifetime indoor exposure at 0.1 ppm are mentioned by Nielsen and Wolkoff (2010). These authors also briefly mention the challenge of the robustness of this model by Subramaniam et al. (2007, 2008) and Crump et al. (2008) including responses of Conolly et al. (2009) and Crump et al. (2009). But notwithstanding these critiques, it has to be acknowledged that this model was the only one trying to include the wealth of data available for a risk assessment of FA.

Epidemiological findings:

The increased risk of nasopharyngeal carcinoma induced by FA in exposed workers, if any, could be based on similar mechanisms as the experimental inductions of nasal tumours in rats. On one hand, dosimetry models have indicated that human nasal flux patterns shifted distally as inspiratory flow rate increased (Kimbell et al, 2001b), on the other hand it appears important that the rat breathes only through the nose while humans, especially upon physical work, show considerable mouth breathing in addition. As a further theory, a contribution of Epstein-Barr virus infections to nasopharyngeal carcinogenesis has been discussed. In essence, it may be concluded that the dose-response of human nasopharyngeal tumours elicited by FA must be non-linear at low doses, based on the modes of action established experimentally in rodents.

A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA. No significant changes in formate excretion could be detected over a 3-week period of exposure to FA at a concentration in air of less than 0.4 ppm (Gottschling et al., 1984; IARC, 2006). This indicates that the physiological homeostasis of endogenous FA is not challenged within this range of external exposure, and consequently, no systemic effects can be expected under such exposure conditions. These considerations are supported by exposure modellings based on data in different species (Heck and Casanova, 2004). In total, there is no biological plausibility for an induction of human leukaemia by formaldehyde exposure (Gentry et al. 2013).

Integrating toxicokinetics and mode of action

Andersen *et al* (2010) combined studies with different FA exposure levels and exposure duration with toxicokinetic modelling for tissue FA acetal and glutathione levels and with histopathology and gene expression in nasal epithelium from rats exposed to 0, 0.7, 2, 6, 10 or 15 ppm FA 6 hours/day for 1, 4 or 13 weeks. At 0.7 and 2 ppm FA, the cellular levels of FA acetal showed a very minor increase with exposures and GSH a very minor decrease; several ppm FA would be required to achieve significant changes. Treatment-related nasal lesions were found in the respiratory epithelium at 2 ppm FA and higher. Patterns of gene expression varied with concentration and duration. At 2 ppm, sensitive response genes associated with cellular stress, thiol transport/reduction, inflammation and cell proliferation were up-regulated at all exposure durations. At 6 ppm and higher, gene expression changes showed enrichment of pathways involved in cell cycle, DNA repair, and apoptosis. ERBB, EGFR, WNT, TGF-β, Hedgehog, and Notch signalling were also enriched. Benchmark doses for significantly enriched pathways were lowest at 13 weeks. Seven genes were combined in a grouping referred to as the "Sensitive Response Genes", showing a benchmark dose around 1 ppm for all three exposure periods. Transcriptional and histological changes at 6 ppm and greater corresponded to dose ranges in which the toxicokinetic model predicted significant reductions in free glutathione levels and increases in FA acetal levels. Genomic changes at 0.7–2 ppm likely represent changes in extracellular FA acetal and glutathione levels. DNA replication stress, enhanced proliferation, squamous metaplasia, and stem cell niche activation appear to be associated with FA carcinogenesis. It was concluded that dose dependencies, high background levels of FA acetal, and nonlinear FA acetal/glutathione tissue kinetics indicated that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells. Overall, this conclusion is in agreement with a histologic NOAEC of 1 ppm for a 2-year inhalation in rats (Woutersen et al, 1989; Gelbke et al, 2014).

Lu et al. (2010a) applied liquid chromatography-tandem mass spectrometry methods to experimental $^{13}CD_2$ FA exposures, allowing differentiation of DNA adducts and DNA-DNA crosslinks originating from endogenous and inhalation-derived FA exposure. Exogenous FA induced N^2-hydroxymethyl-deoxyguanosine (dG) mono-adducts and dG-dG crosslinks in DNA from rat respiratory nasal mucosa, but did not form $^{13}CD_2$-adducts in sites remote to the portal of entry. No N^6-$HO^{13}CD_2$-deoxyadenosine (dA) adducts were detected in nasal DNA. In contrast, high amounts of endogenous FA dG and dA mono-adducts were present in all tissues examined. The number of exogenous N^2-$HO^{13}CD_2$-dG in 1- and 5-day nasal DNA samples from rats exposed to 10 ppm $^{13}CD_2$-FA was 1.28 ± 0.49 and 2.43 ± 0.78 adducts/10^7 dG, respectively, while 2.63 ± 0.73 and 2.84 ± 1.13 N^2-$HOCH_2$-dG endogenous adducts/10^7 dG and 3.95 ± 0.26 and 3.61 ± 0.95 N^6-$HOCH_2$-dA endogenous adducts/10^7 dA were present. The results were interpreted to provide strong evidence in support of a genotoxic and cytotoxic mode of action for the carcinogenesis of inhaled FA in respiratory nasal epithelium, but of no support of a biological plausibility that inhaled FA causes leukaemia.

In a consecutive study of Lu et al, (2011), endogenous and exogenous N^2-hydroxymethyl-dG adducts in nasal DNA of rats exposed to 0.7, 2, 5.8, 9.1 or 15.2 ppm $^{13}CD_2$ for 6 hours were quantified by a highly sensitive nano-UPLC-MS/MS (ultra-performance liquid chromatography tandem mass spectrometry) method. Exogenous FA DNA adducts were formed in a highly non-linear fashion, with a 21.7-fold increase in exposure causing a 286-fold increase in exogenous adducts (see *Figure 1*). Endogenous DNA adducts dominated at low exposures, comprising more than 99 % of total adduct levels. In contrast, exogenous adducts were not detectable in the bone marrow of rats exposed to 15.2 ppm $^{13}CD_2$. In this context, it was demonstrated that N^2-hydroxymethyl-dG was the primary DNA adduct formed in nasal cells following FA exposure while endogenous FA also led to the corresponding dA-adducts in amounts comparable to endogenous dG-adducts. Also in monkeys exposed to 2 or 6 ppm, 6 hours/day for 2 days, the external FA-dG adduct was only detected in the nose and not in the bone marrow. At 6 ppm, the FA-dG adduct level was lower in the nasal tissue in the monkeys

ED_014350_00001020-00047

than in rats with a single 6-hour exposure, suggesting a lower risk in primates than in rats (Moeller et al, 2011).

Swenberg et al. (2011) compared endogenous and exogenous FA induced DNA-dG adducts in the nasal tissue of primates and rats. Exogenous adducts in monkeys after 2 days of exposure were similar to those of rats exposed for 1 day at 2 ppm and were ~2.5 times lower in monkeys at 6.1 ppm for 2 days compared to rats at 5.8 ppm for 1 day (6 h/d). These data demonstrate that exogenous adducts formed in the nasal turbinates are lower for nonhuman primates than for rats. In addition, there are indications that endogenous dG adducts are 2-3-fold higher in monkeys than in rats. This reduces the ratio of exogenous/endogenous adducts in primates exposed to low FA concentrations by a factor of ~5.

Yu et al. (2015) determined formation, accumulation, and hydrolysis of endogenous and exogenous FA DNA adducts in rats after exposure to 2 ppm over 28 consecutive days (6 h/d) followed by a 7 day post-exposure period. Monkeys were exposed to 6 ppm on 2 consecutive days (6 h/d) and DNA dG adducts were measured in different parts of the respiratory tract. Again exogenous DNA adducts were only found in nasal tissue of rats and monkeys. In the lower respiratory tract no exogenous adducts could be measured in the trachea or carina (monkeys). The exogenous dG FA adducts in rats approached a steady state concentration during the 28 d exposure period with a rapid loss of nearly 20% during the first 6 h post exposure followed by a much slower decrease thereafter. The half-life for formation and loss of the exogenous adducts was estimated to be 7.1 days. Combining the data for monkeys in the present study with those of Moeller et al. (2011) showed that exogenous adducts in different sections of the nasal epithelium were always 5-11-fold lower than endogenous adducts.

Yu et al. (2015) also studied the relationship between the formation of FA DNA adducts and DPX. After Lu et al. (2009) had shown that FA readily reacts with the thiol group of GSH to form a crosslink with N^2-dG via a methylene group, Lu et al. (2010a,b) systematically studied crosslinking reactions of FA with different amino acids and nucleosides. The highest yields of cross-linked products were obtained with FA + lysine + dG followed by the reaction with cysteine and dG. Yields from the other reaction partners were lower by a factor of 10 or more. While the lysine adduct was unstable at ambient temperature, that derived from cysteine was stable. Based on these findings Yu et al. (2015) showed that the N^2-dG-methylene adducts with cysteine and GSH were unstable at physiological pH and room temperature with a half-life of 11.6 min and 79.6 min, respectively. Cleavage occurred at the methylene-S-bond but not at the N^2-dG-methylene bond leading to the N^2-hydroxymethyl-dG adduct identified in former investigations (Lu et al, 2010a,b, 2011, 2012; Moeller et al, 2011). These results suggested that DPXs may be important sources of FA induced DNA mono adducts.

In the light of the instability of FA induced DPXs the authors questioned the reported increase of DPXs after FA exposure in circulating lymphocytes in workers (Shaham et al., 1996, 2003) or in several tissues of mice (Ye et al., 2013). They proposed that these unexpected findings may be due to the use of non-specific DPX assays that cannot differentiate between exogenous and endogenous FA induced DPXs.

At an exposure level of 2 ppm Yu et al. (2015) have shown that FA-dG adducts accumulate to reach a steady state after 28 days. By combining the data of Lu et al. (2011) for a single exposure to 0.7 and 2 ppm with those of Yu et al. (2015) at 2 ppm over 28 days the exogenous steady state DNA adduct levels at 0.7 ppm may be approximated. Exogenous adducts at 2 ppm, single exposure, were 0.19 adducts/10^7 dG and after 28 days 1.05 (factor of 5.5). At 0.7 ppm, single exposure, 0.039 exogenous adducts/10^7 dG were found and therefore at steady state after 28 days of 0.21 adducts/10^7 dG might be expected. A direct comparison with endogenous adducts is somehow hampered because there was a difference between both of the studies: mean endogenous adducts 4.57 adducts/10^7 dG for Lu et al (2011) and 2.91 for Yu et al (2015). But the steady state exogenous adducts of about 0.2 adducts/10^7 dG were by a

factor of 14 or 22 lower than the endogenous adducts. In addition, these exogenous steady state adducts were always within the standard deviations of both studies (Lu et al, 2011; Yu et al, 2015). Taking into account the low dose non-linearity of the response curve for exposures below 0.7 ppm (for example at 0.3 ppm) a more than proportional decrease of exogenous adducts is to be expected.

Overall, the use of highly sensitive LC-MS/MS and isotope labelled compounds for exposure provided relevant new mechanistic insights into the formation and role of FA-derived DNA adducts (Lu et al, 2012) and furthermore indicating that inhaled FA does not reach the blood compartment or the internal organs in experimental animals.

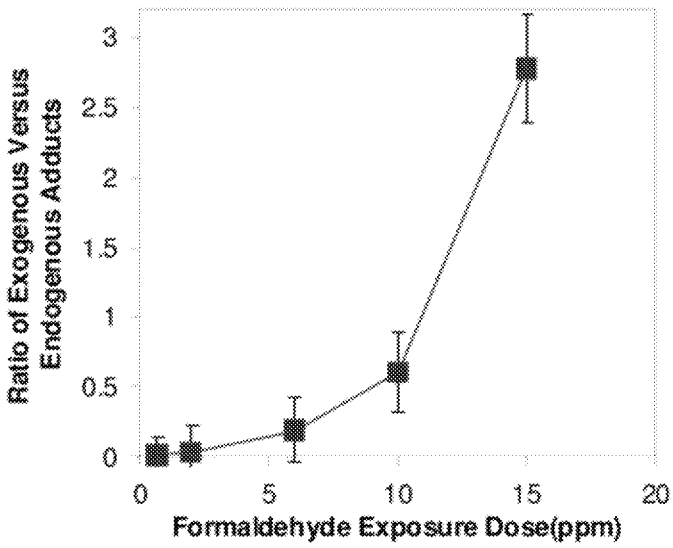


Figure 1. Exposure-response of ratios of exogenous/endogenous FA-DNA adducts in nasal epithelium of rats exposed to [13CD2]-FA for 6 hours (from Lu et al., 2011; material in public domain)

Starr and Swenberg (2013) proposed a bottom-up approach for assessment of low dose human cancer risk from exposure to chemicals that produce the same specific DNA adducts from endogenous and exogenous sources. Taking into account background (endogenous) exposure the approach is consistent with the "additivity to background concept" and provides central and upper bound risk estimates that are linear at all doses. The endogenous and exogenous dG adducts of FA measured in Cynomolgus macaques (Moeller at al, 2011) at 2 ppm after two 6 h exposures were taken as a surrogate for humans for continuous life-time exposure. The build-up of adducts was estimated by kinetic modelling of the Swenberg et al. (2013) rat data yielding an elimination half-life of 63 h. Thereby they arrived at an upper bound life time risk of 3.8×10^{-4} for continuous exposure at 1 ppm. This risk estimate is nearly 29-fold lower than that calculated by the approach of the U.S. EPA (1.1×10^{-2}). For exposure at the workplace a simple linear modelling would then result in an upper bound risk at 0.3 ppm of 1.6×10^{-5} (exposure of 5 d/week, 8 h/d over 45 years). The authors noted several reasons why their model should be considered conservative, because for example all background risks for NPC are only ascribed to dG adducts (and not also to the endogenous dA adducts not formed by exogenous FA) or linearity is assumed for all exposure levels without taking into consideration cytotoxicity or cell proliferation enhancing mutations. On the other hand, the half-life of dG adducts has recently been shown to be longer, i.e. 7.1 d about 2.7-fold higher than the half-life used in this extrapolation (Yu et al., 2015).

FA is a major source of N^6-formyllysine ("FA-Lys") adducts in cell proteins. In rats, exposures to isotope labelled FA ($^{13}C^2H_2O$) at 0.7, 2, 6 and 9 ppm for 6 hours were used in differentiating between adducts from exogenous and endogenous FA-Lys adducts in the total, the cytoplasmic, the membrane and the nuclear proteins. After proteolysis and analysis of FA-Lys, the ratio between exogenous and endogenous adducts was shown to increase with increasing exposure; for example for the total nasal epithelial proteins, the ratio was 0.035, 0.14, 0.15 and 0.40, respectively. At each of these FA exposures, the ratios were in the order cytoplasmic ≈ membrane > soluble nuclear > chromatin protein bound, indicating a decrease in the exogenous FA concentration from the cytoplasmic to the nuclear proteins. Opposite, the endogenous FA-Lys adducts were similar at all exposure concentrations in all cellular compartments. Also, this indicated that the external FA exposure did not influence the endogenous FA production. No external FA-Lys adducts were detected in the lungs, liver and bone marrow and thus, the results paralleled studies on FA-dG adducts, confirming that direct external FA adducts are limited to the nasal epithelium (Edrissi et al., 2013).

In view of a discussion of an association of FA with the development of leukaemia, Kleinnijenhuis et al. (2013) performed an inhalation experiment with FA in rats, in order to study whether FA can enter the blood and thus cause systemic toxicity in remote tissues. To differentiate between exogenous and endogenous FA, the rats were exposed (10 ppm for 6 hours) to stable isotope ^{13}C-labelled FA by inhalation. During and after exposure, blood was analysed to determine the ratio between labelled and endogenous FA in blood and the total blood concentration of FA. With the method applied, exogenous ^{13}C-FA could have been detected in blood at a concentration approximately 1.5 % of the endogenous FA blood concentration. However, exogenous ^{13}C-FA was not detectable in the blood of rats, neither during nor up to 30 min after the exposure. It was concluded that the inhalation of FA, even at 10 ppm for 6 hours, did not result in an increase of the total FA concentration in blood.

Rager et al. (2014) investigated microRNA responses to FA. Rats were exposed by inhalation to either 0 or 2 ppm FA for 7, 28 or 28 days followed by a 7-day recovery. Genome-wide microRNA expression profiles were assessed within the nasal respiratory epithelium, circulating leukocytes and bone marrow. MicroRNAs showed altered expression in the nose and leukocytes but not in the bone marrow. In the nose, microRNA 10b and members of the let-7 family, known nasopharyngeal carcinoma players, showed decreased expression. Genome-wide messenger RNA profiles were assessed in the nose and leukocytes. Pathway analyses revealed an enrichment of immune system/inflammation signalling in the nose and leukocytes. Specific to the nose was enrichment for apoptosis/proliferation signalling, involving let-7a, let-7c, and let-7f. Across all tissues and time points assessed, microRNAs were predicted to regulate between 7 % and 35 % of the transcriptional responses and were suggested to play a role in signalling processes including immune/inflammation-related pathways. The data were interpreted to confirm the concept that FA-induced inflammatory signals originating in the nose may drive leukocyte effects.

In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat. New data support the view (Heck and Casanova, 2004) that there is no delivery of inhaled FA to distant sites of the organism. A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013).

7.10. Lack of specific scientific information

No specific lack of data or information was identified.

ED_014350_00001020-00050

7.11 Recommendation, health considerations

The primary aim of an Occupational Exposure Limit (OEL) for FA is to avoid upper respiratory tract cancer as has been observed in rodents, especially in rats at exposure concentration of ≥6 ppm. In addition an OEL should also protect against undue annoyance for the worker population. Tumour induction by FA is driven by sustained cytotoxicity and cell proliferation while genetic changes are secondary (McGregor et al., 2006). Therefore for FA a threshold can be established for concentrations not leading to such sustained cell proliferation and histopathological alterations. A NOAEC has been established in the sensitive rat for histopathological alterations at 1 ppm and for regenerative cell proliferation based on the large experimental database (Gelbke et al., 2014). Under these considerations FA is considered a group C carcinogen (genotoxic carcinogens for which a practical threshold is supported; Bolt and Huici-Montagud, 2008; SCOEL, 2013). This classification corresponds closely to that of the German MAK commission (DFG, 2015) as a group 4 carcinogen.

Data pivotal for the derivation of an OEL, namely the NOAEC for sustained cytotoxic irritation, are only available for experimental animals, but not for humans for ethical reasons. The rat is a poor and most probably over-sensitive model in this respect due to its different respiratory physiology while the monkey exhibits many similarities to humans (DeSesso, 1993). There are clear indications that the monkey is less sensitive than the rat if FA-DNA adducts (Moeller et al, 2011, Swenberg et al, 2011) or DNA-protein-crosslink (DPX) formation (Casanova et al, 1991) are taken as indicator for target tissue exposure. Humans are likely to be even less sensitive than monkeys (Casanova et al, 1991).

On the other hand, there is a solid database for humans (comprising in total more than 400 volunteers) for sensory irritation of FA on the eye, a very sensitive parameter (DECOS 2003, Nordic Expert Group 2003). It is generally considered that avoidance of sensory irritation of the eye and the upper respiratory tract would automatically imply a safety margin to also avoid cytotoxic irritation-induced local cell proliferation as a first step to tumour induction. Derivation of an OEL based on sensory eye irritation in humans inherently provides a broad margin of safety in comparison to the induction of upper respiratory tract tumours in rats for the following reasons:

- Sensory irritation occurs at lower concentrations than cytotoxic irritation (Brüning et al, 2014).
- Due to confounding factors, like personality traits or odour, subjective symptoms of irritation (as generally only measured in pre-2000 studies) tend to overestimate sensory irritation as measured by objective parameters.
- In humans sensory irritation to the eyes occurs at lower concentrations than sensory irritation to the respiratory tract, the potential target for FA induced tumours (Brüning et al, 2014).
- Due to the differences in respiratory physiology rats are more sensitive than monkeys and monkeys probably more sensitive than humans with regard to DPX formation (Casanova et al, 1991).
- The amount of DNA adducts is higher in rats than in monkeys at comparable exposure concentrations and especially also the ratio of exogenous/endogenous adducts (Swenberg et al, 2011).
- One important aspect has to be taken into consideration for all extrapolations from high dose experimental data to low human exposures, namely the steep upward bent dose response curve, being most pronounced at concentrations

≥2 ppm, for all decisive parameters, like tumour incidences (Kerns et al, 1983; Monticello et al., 1997), cell proliferation (Monticello et al, 1997), DPX formation (Casanova et al., 1991) and dG adducts (Lu et al., 2011). Also cell proliferation (as measured by PWULLI – Population-Weighted Unit Length Labelling Index) vs. %-tumour rate shows a steep upward bent relationship (Monticello and Morgan, 1997).

- This dose response relationship has also been found by in vitro genotoxicity studies (Speit et al, 2007).

Although it has to be acknowledged that these points cannot be quantitatively agglomerated to a numerical uncertainty factor (in the sense of SCOEL, 2013), SCOEL will primarily base its considerations on objective parameters for sensory irritation obtained by human volunteer studies.

Former studies (up to 2008) mainly relied on self-reported symptoms of volunteers exposed to defined concentrations of FA. On the basis of these studies concentrating on a total of 17 high-quality controlled studies with volunteers it was concluded by an independent expert panel convened in the USA by the Industrial Health Foundation (IHF) that with daily exposure for 8 hours to maximum FA concentrations of 0.3 ppm "practically all workers" are protected against eye irritation. Animal data were considered supportive of this conclusion. In consequence, a concentration of 0.3 ppm FA was regarded as a practical NOAEC and was proposed as an OEL (Paustenbach et al, 1997).

By contrast, the identical database for sensory irritation of FA, as compiled by Paustenbach et al (1997), was viewed by the joint DECOS (2003) and Nordic Expert Group (2003) committees to reveal that "at lower exposure levels sensory irritation may still occur in a substantial percentage of exposed individuals". The joint committees regarded 0.24 ppm (see below) FA to be a LOAEC "at which sensory irritation may occur in a low but significant percentage of exposed workers". At the same time, it was stated that the majority of short- and long-term animal inhalation studies reveal a NOAEC of 1-2 ppm, with slight histopathological changes of the nasal respiratory epithelium being observed at 0.3-2 ppm (Kamata et al, 1997). But as shown above this study may not be taken as evidence for a NOAEC in experimental animals of <1 ppm. On this basis, DECOS (2003) recommended a health-based OEL (TWA) of 0.12 ppm (0.15 mg/m^3), with a STEL of 0.42 ppm (0.5 mg/m^3).

This discrepancy in evaluations of an identical data set by the IHF *vs*. DECOS/Nordic Expert groups is mainly influenced by interpretation of two studies from Scandinavia.

The first was a field study on FA-induced discomfort (Wilhelmsson and Holmström, 1992) that was not included in the evaluation by the IHF group, but was considered as a "not well-documented study" by the joint DECOS/Nordic group, showing that "more than 50% of 66 occupationally exposed workers complained of nasal discomfort after long-term exposure to an average concentration of 0.26 mg/m^3 (0.22 ppm; range 0.05-0.6 mg/m^3 or 0.04-0.5 ppm)". In a reference group, 25% gave such reportings (Wilhelmsson and Holmström, 1992). However, the publication neither gives methodological details of the questionnaire used, nor was the way of exposure assessment specified.

The second was a controlled study in volunteers (Andersen and Mølhave, 1983) in which 3 out of 16 subjects reported eye irritation at a FA concentration of 0.24 ppm (see above). This study has the fundamental weakness that no control group with sham exposure was included while Arts et al. (2006) and Paustenbach et al. (1997) observed that in control groups exposed to 0 ppm 15-22% of the participants will report slight eye irritation. Whereas the joint DECOS/Nordic Export groups took this as a hint to sensory irritation in substantial percentages of individuals at less than 0.3 ppm FA, the IHF group's argumentation was based on a concentration-response curve constructed from the entire body of data from the reported irritation studies. According to their evaluation irritation reportings may be obtained in 15-20% of non-exposed volunteers as well

(Paustenbach et al. 1997). Arts et al. (2006) applied a benchmark approach to the study of Andersen and Mølhave (1983) and arrived at the conclusion that a concentration of 0.24 ppm FA, based on slight subjective discomfort, a 95% confidence interval, and assuming a background response of 1/16 (6.25%), would be acceptable.

With the availability of two volunteer exposure studies complementing each other and not only measuring subjective reportings but also objective signs of eye and upper respiratory tract irritation (Lang et al., 2008; Mueller et al., 2013), an OEL can now be based on objective parameters not potentially biased by personality traits like anxiety or expectations. Such factors will not play a role for subjects used to work with FA. A synopsis of both studies leads to a NOAEC for objective parameters of sensory irritation of 0.7 ppm or 0.4 ppm with peaks of 0.8 ppm. Both studies applied slightly different concentration regimes. Exposures with 4 superimposed peaks being most relevant for derivation of an OEL with STEL were 0.3 ppm + peaks of 0.6 ppm and 0.5 ppm + peaks of 1 ppm in the Lang study, and in that of Mueller 0.3 ppm + peaks of 0.6 ppm and 0.4 ppm + peaks of 0.8 ppm. Objective signs of irritation were only observed at 0.5 ppm + peaks of 1 ppm. Because 0.3 ppm + peaks of 0.6 ppm was a consistent NOAEC in both of these investigations this exposure regime is proposed as the basis for an OEL with STEL. This NOAEC based on 62 volunteers (41 in the Mueller study and 21 in the Lang study) is sufficiently robust for the derivation of a Limit Value. No further uncertainty factor for possible human inter-individual variations is necessary, especially as low interindividual variation is also confirmed by the older studies reviewed by Paustenbach et al. (1997). Thus for high quality volunteer studies, Brüning et al. (2014) recently concluded that an OEL may be based on the NOAEC without an additional safety factor. Also, these authors propose an interspecies extrapolation factor of 3 for extrapolating animal data to humans concerning local irritation effects, but this may be reduced to 2 because of existing modellings of the airway physiology and FA deposition of rats and humans. Starting from the NOAEC of 1 ppm in rats this would lead to 0.5 or 0.3 ppm similar to the NOAECs found in human volunteers.

In conclusion, SCOEL recommends a Limit Value of 0.3 ppm (8 h TWA) with a STEL of 0.6 ppm corresponding to the NOAECs for objective signs of sensory irritation in human volunteer studies. An additional uncertainty factor according to SCOEL (2013) is not used as no corresponding factors need to be covered in addition and since the critical effect has been studied with essentially the same results in many investigations, including the older ones concentrating on subjective symptoms.

This 8 h TWA is further supported by risk extrapolations from experimental animals to humans (Conolly et al., 2004; Andersen et al., 2010; Starr and Swenberg, 2013).

Finally it needs to be addressed whether the recommended Limit Value of 0.3 ppm (8 h TWA) with 4 peaks of 0.6 ppm (STEL) will also protect from irritation and undue annoyance [in the sense of "nuisance" according to SCOEL (2013)]. No subjective symptoms of irritation were observed by Mueller et al. (2013) up to the highest exposure. In contrast, in the study of Lang et al. (2008) subjective symptoms were already reported at concentrations as low as 0.3 ppm. But when negative affectivity was used as covariate the only effect level was 0.5 ppm + peaks at 1 ppm as for objective signs of irritation. As negative affectivity will not play a decisive role at the workplace, these findings for subjective symptoms of irritation have to be considered as grade (1) or at most between grade (1) and (2) (SCOEL, 2013; chapter 3.1).

Odour perception was reported in both studies. This was statistically significantly increased in Lang et al. (2008) at ≥0.3 ppm but the odour of 12-16 ppm ethyl acetate was perceived stronger than that at 0.5 ppm and similar to that at 0.5 ppm + peaks of 1 ppm FA. Similar results were reported for annoyance. In the study of Mueller et al. (2013) again significant differences were noted for olfactory symptoms without a concentration effect relationship and especially for the "perception of impure air", most pronounced in the group of hypersensitive persons against CO_2 nasal irritation. Olfactory symptoms were dominated by "perception of impure air". For the complaint "perception

of impure air" a statistically significant increase was already noted at 0 ppm (pre- vs. end of exposure) in hypersensitive persons. Therefore this item cannot be ascribed to FA only. Because a statistically significant difference in symptom scores between FA exposures and control conditions was missing, the authors concluded that the increase in olfactory symptoms is mainly induced by displeasing ambient smell and the situational and climatic conditions in the exposure chamber. Again FA related olfactory symptoms and "perception of impure air" may at most reach a grading between (1) and (2) according to SCOEL (2013; chapter 3.1).

In conclusion, a Limit Value of 0.3 ppm with a STEL of 0.6 ppm will also protect from "nuisance" at the workplace caused by subjective symptoms of irritation and odour.

It is noted that that the Limit Value of 0.3 ppm with a STEL of 0.6 ppm deviates from the "preferred value" concept of SCOEL (2013) using decimals of integers 1, 2, or 5 ppm. This deviation is scientifically justified as the derivation of the Limit Value is based on an exceptionally broad database of actual NOAECs from human volunteer studies.

As explained in chapter 7.9, a possible induction of myeloid leukaemia by FA in humans would require that FA acts systemically and thereby reaches the bone marrow, which is the target tissue for leukaemia. Such a systemic toxicity is not possible within the exposure range where the external FA dose does not change the internal physiological level of FA, i.e., less at exposures up to 0.4 ppm. This means that the human physiological homeostasis of endogenous FA is not challenged within the range of the proposed OEL, and consequently, that no systemic effects can be expected under such exposure conditions.

8. Groups at extra Risk

FDH is the most important and highly efficient enzyme for detoxification of FA, thereby safeguarding especially against its genotoxicity and carcinogenicity. This essential enzyme is highly conserved in all species. A broad database has demonstrated that in the normal European population no polymorphism exists with impaired FA detoxification. As already discussed in detail in section 7.5.1, FA does not induce or exacerbate asthma in asthmatics at FA concentrations below 1 ppm. Thus, there is no support that asthmatics were at extra risk at relevant concentrations.

ED_014350_00001020-00054

9. References

AFNOR NFX 43-264 (2002) Normes préparées ou examinées par la commission X43C « Air des lieux de travail (code ICS 13.040.30). http://www.afnor.fr. Accessed 04.24.2016

AFSSET (2008) Valeurs limites d'exposition en milieu professionnel Évaluation des effets sur la santé et des methods de mesure des niveaux d'exposition sur le lieu de travail pour le formaldehyde. https://www.anses.fr/en/system/files/VLEP2008etFormaldhehydeRa.pdf Accessed 04.25.2016

Alderson, T. (1965). Chemically induced delayed germinal mutation in Drosophila. Nature, 207, 164-7.

Alderson, T. (1985). Formaldehyde-induced mutagenesis: a novel mechanism for its action. Mutat Res, 154, 101-10.

Andersen, M. E., Clewell, H. J., Bermudez, E., Dodd, D. E., Willson, G. A., Campbell, J. L., Thomas R. S. (2010). Formaldehyde: Integrating dosimetry, cytotoxicity, and genomics to understand dose-dependent transitions for an endogenous compound. Toxicol Sci, 118, 716–31.

Andersen, I., Mølhave, L. (1983). Controlled human studies with formaldehyde. In: Gibson, J.E. (ed.) Formaldehyde Toxicity, 154-165. Washington: Hemisphere Publishing Corporation.

Armstrong, R. W., Imrey, P. B., Lye, M. S., Armstrong, M. J., Yu, M. C.,Sani, S. (2000). Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Int J Epidemiol, 29, 991-8.

Arts, J. H., Rennen, M. A., De Heer, C. (2006). Inhaled formaldehyde: evaluation of sensory irritation in relation to carcinogenicity. Regul Toxicol Pharmacol, 44, 144-60.

ASTM (2009). ASTM D5197-09e1, Standard Test Method for Determination of Formaldehyde and Other Carbonyl Compounds in Air (Active Sampler Methodology), ASTM International, West Conshohocken, PA, 2009, http://www.astm.org/Standards/D5197

ATSDR (Agency for Toxic Substances and Disease Registry) (1999). Toxicological Profile for Formaldehyde. Public Health Service, US Department of Health & Human Services.

Aydin, S., Canpinar, H., Undeger, U., Guc, D., Colakoglu, M., Kars, A., Basaran, N. (2013). Assessment of immunotoxicity and genotoxicity in workers exposed to low concentrations of formaldehyde. Arch Toxicol, 87, 145-53.

Bachand, A. M., Mundt, K. A., Mundt, D. J., Montgomery, R. R. (2010). Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: a meta-analysis. Crit Rev Toxicol, 40, 85-100.

Ballarin, C., Sarto, F., Giacomelli, L., Bartolucci, G. B., Clonfero, E. (1992). Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. Mutat Res, 280, 1-7.

Barrow, C.S., Steinhagen, W.H., Chang J.C.F. (1983). Formaldehyde sensory irritation. In: Je, G. (ed.) Formaldehyde Toxicity. Washington, New York, London: Hemisphere Publishing Corp.

Barrow Cs, B. L., Buckley, L.A., James R.A., Steinhagen W.H.,, Chang J.C.F. (1986). Toxicology of the Nasal Passages, Sensory irritation: studies on

ED_014350_00001020-00055

correlation to pathology, structure-activity, tolerance development, and prediction of species differences to nasal injury. Washington, New York, London: Hemisphere Publishing Corp.

BAUA (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin) (2006). TRGS 900 "Arbeitsplatzgrenzwerte". http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-900.html

Bauchinger, M., Schmid, E. (1985). Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. Mutat Res, 158, 195-9.

Beane Freeman, L. E., Blair, A., Lubin, J. H., Stewart, P. A., Hayes, R. B., Hoover, R. N., Hauptmann, M. (2009). Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst, 101, 751-61.

Beane Freeman, L. E., Blair, A., Lubin, J. H., Stewart, P. A., Hayes, R. B., Hoover, R. N., Hauptmann, M. (2013). Mortality from solid tumors among workers in formaldehyde industries: an update of the NCI cohort. Am J Ind Med, 56, 1015-26.

BEK (2011). Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer. BEK nr 1134 af 01/12/2011 (Gældende). Ministerium: Beskæftigelsesministeriet Journalnummer: Beskæftigelsesmin., Arbejdstilsynet, j.nr. 2011007144. https://www.retsinformation.dk/pdfPrint.aspx?id=139131

Belgium (2014). Revised version valid for after July 2014. In dutch. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk. https://www.google.it/?gfe_rd=cr&ei=2v00Vb7xC6fD8ges7oHQAw&gws_rd=ssl#q=Koninklijk+besluit+van+11+maart+2002+betreffende+de+bescherming+van+de+gezondheid+en+de+veiligheid+van+de+werknemers+tegen+de+risico%E2%80%99s+van+chemische+agentia+op+het+werk

Bender, J. (2002). The use of noncancer endpaints as a basis for establishing a reference concentration for formaldehyde. Reg Toxicol Pharmacol 35, 23-31.

Benkmann, H.G., Agarwal, D.P., Saha, N., Goedde, H.W. (1991). Monomorphism of formaldehyde dehydrogenase in different populations. Hum Hered, 41, 276-8.

Berglund, B., Höglund, A., Esfandabad, H. (2012). A bisensory method for odor and irritation detection of formaldehyde and pyridine. Chemosensory Perception, 5, 146-157.

Bizzari, 2007. CEH Marketing Research Report: Formaldehyde." 658.5000 A. SRI International. 106 pp. ' http://chemical.ihs.com/nl/Public/2007Mar.pdf

Bogdanffy, M. S., Morgan, P. H., Starr, T. B., Morgan, K. T. (1987). Binding of formaldehyde to human and rat nasal mucus and bovine serum albumin. Toxicol Lett, 38, 145-54.

Bolt, H. M. (1987). Experimental toxicology of formaldehyde. J Cancer Res Clin Oncol, 113, 305-9.

Bolt, H. M., Huici-Montagud, A. (2008). Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol, 82, 61-4.

ED_014350_00001020-00056

Bolt, H. M., Morfeld, P. (2013). New results on formaldehyde: the 2nd International Formaldehyde Science Conference (Madrid, 19-20 April 2012). Arch Toxicol, 87, 217-22.

Bouraoui, S., Mougou, S., Brahem, A., Tabka, F., Ben Khelifa, H., Harrabi, I., Mrizek, N., Elghezal, H., Saad, A. (2013). A combination of micronucleus assay and fluorescence in situ hybridization analysis to evaluate the genotoxicity of formaldehyde. Arch Environ Contam Toxicol, 64, 337-44.

Brüning, T., Bartsch, R., Bolt, H. M., Desel, H., Drexler, H., Gundert-Remy, U., Hartwig, A., Jäckh, R., Leibold, E., Pallapies, D., Rettenmeier A. W., Schlüter, G., Stropp, G., Sucker, K., Triebig, G., Westphal, G., Van Thriel, C. (2014). Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol. 88, 1855-1979

Casanova, M., Heck H. D., A. (1987). Further studies of the metabolic incorporation and covalent binding of inhaled [3H]- and [14C]formaldehyde in Fischer-344 rats: effects of glutathione depletion. Toxicol Appl Pharmacol, 89, 105-21.

Casanova, M., Heck, H. D., Everitt, J. I., Harrington, W. W., Jr., Popp, J. A. (1988). Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. Food Chem Toxicol, 26, 715-6.

Casanova, M., Deyo, D. F., Heck, H. D. (1989). Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic interpretation. Fundam Appl Toxicol, 12, 397-417.

Casanova, M., Morgan, K. T., Steinhagen, W. H., Everitt, J. I., Popp, J. A., Heck, H. D. (1991). Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. Fundam Appl Toxicol, 17, 409-28.

Casanova, M., Morgan, K. T., Gross, E. A., Moss, O. R., Heck, H. A. (1994). DNA-protein cross-links and cell replication at specific sites in the nose of F344 rats exposed subchronically to formaldehyde. Fundam Appl Toxicol, 23, 525-36.

Casanova, M., Heck, H. D., Janszen, D. (1996). Comments on 'DNA-protein crosslinks, a biomarker of exposure to formaldehyde--in vitro and in vivo studies' by Shaham et al. Carcinogenesis, 17, 2097-101.

Casanova-Schmitz, M., Heck, H. D. (1983). Effects of formaldehyde exposure on the extractability of DNA from proteins in the rat nasal mucosa. Toxicol Appl Pharmacol, 70, 121-32.

Casanova-Schmitz, M., Starr, T. B., Heck, H. D. (1984). Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [14C]- and [3H]formaldehyde. Toxicol Appl Pharmacol, 76, 26-44.

Cassee, F.R. (1995). Upper Respiratory Tract Toxicity of Mixtures of Aldehydes. Doctoral thesis, University of Utrecht, NL.

Cassee, F. R., Arts, J. H., Groten, J. P., Feron, V. J. (1996). Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. Arch Toxicol, 70, 329-37.

ED_014350_00001020-00057

Casset, A., Marchand, C., Purohit, A., le Calve, S., Uring-Lambert, B., Donnay, C., Meyer, P., de Blay, F. (2006). Inhaled formaldehyde exposure: effect on bronchial response to mite allergen in sensitized asthma patients. Allergy, 61, 1344–50.

Castle, S.L., Board, P.G. (1982). Electrophoretic investigation of formaldehyde dehydrogenase from human tissues. Hum Hered, 32, 222-4.

Chang, J. C., Steinhagen, W. H., Barrow, C. S. (1981). Effect of single or repeated formaldehyde exposure on minute volume of B6C3F1 mice and F-344 rats. Toxicol Appl Pharmacol, 61, 451-9.

Chang, J. C., Barrow, C. S. (1984). Sensory irritation tolerance and cross-tolerance in F-344 rats exposed to chlorine or formaldehyde gas. Toxicol Appl Pharmacol, 76, 319-27.

Checkoway, H., Boffetta, P., Mundt, D. J., Mundt, K. A. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. Cancer Causes Control, 23, 1747-66.

CIIT (Chemical Industry Institute of Toxicology) (1999). Formaldehyde: hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation. Research Triangle Park, NC, USA.

Coggon, D., Harris, E. C., Poole, J., Palmer, K. T. (2003). Extended follow-up of a cohort of british chemical workers exposed to formaldehyde. J Natl Cancer Inst, 95, 1608-15.

Coggon, D., Ntani, G., Harris, E. C., Palmer, K. T. (2014). Upper airway cancer, myeloid leukemia, and other cancers in a cohort of British chemical workers exposed to formaldehyde. Am J Epidemiol, 179, 1301-11.

Cole, P., Adami, H. O., Trichopoulos, D., Mandel, J. (2010). Formaldehyde and lymphohematopoietic cancers: a review of two recent studies. Regul Toxicol Pharmacol, 58, 161-6.

Collins, J.J., Ness, R., Tyl, R.W., Krivanek, N., Esmen, N.A., Hall, T.A. (2001). A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. Regul Toxicol Pharmacol 34, 17-34.

Collins, J. J., Lineker, G. A. (2004). A review and meta-analysis of formaldehyde exposure and leukemia. Regul Toxicol Pharmacol, 40, 81-91.

Conolly, R. B., Kimbell, J. S., Janszen, D., Schlosser, P. M., Kalisak, D., Preston, J., Miller, F. J. (2004). Human respiratory tract cancer risks of inhaled formaldehyde: dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. Toxicol Sci, 82, 279-96.

Conolly, R. B., Miller, F. J., Kimbell, J. S. & Janszen, D. 2009. Letter to the Editor. Formaldehyde risk assessment. Ann Occup Hyg 53, 181–9.

Cosma, G. N., Marchok, A. C. (1988). Benzo[a]pyrene- and formaldehyde-induced DNA damage and repair in rat tracheal epithelial cells. Toxicology, 51, 309-20.

Cosma, G. N., Wilhite, A. S., Marchok, A. C. (1988). The detection of DNA-protein cross-links in rat tracheal implants exposed in vivo to benzo[a]pyrene and formaldehyde. Cancer Lett, 42, 13-21.

ED_014350_00001020-00058

Costa, S., Coelho, P., Costa, C., Silva, S., Mayan, O., Santos, L. S., Gaspar, J., Teixeira, J. P. (2008). Genotoxic damage in pathology anatomy laboratory workers exposed to formaldehyde. Toxicology, 252, 40-8.

Costa, S., Pina, C., Coelho, P., Costa, C., Silva, S., Porto, B., Laffon, B. & Teixeira, J. P. 2011. Occupational exposure to formaldehyde: genotoxic risk evaluation by comet assay and micronucleus test using human peripheral lymphocytes. J Toxicol Environ Health A, 74, 1040–51.

Costa, S., Garcia-Leston, J., Coelho, M., Coelho, P., Costa, C., Silva, S., Porto, B., Laffon, B., Teixeira, J. P. (2013). Cytogenetic and immunological effects associated with occupational formaldehyde exposure. J Toxicol Environ Health A, 76, 217-29.

Costa, S., Carvalho, S., Costa, C., Coelho, P., Silva, S., Santos, L. S., Gaspar, J. F., Porto, B., Laffon, B., Teixeira, J. P. (2015). Mutagenesis, Epub ahead of print, doi:10.1093/mutage/gev002

Craft, T. R., Bermudez, E., Skopek, T. R. (1987). Formaldehyde mutagenesis and formation of DNA-protein crosslinks in human lymphoblasts in vitro. Mutat Res, 176, 147-55.

Crosby, R. M., Richardson, K. K., Craft, T. R., Benforado, K. B., Liber, H. L., Skopek, T. R. (1988). Molecular analysis of formaldehyde-induced mutations in human lymphoblasts and E. coli. Environ Mol Mutagen, 12, 155-66.

Crump, K. S., Chen, C., Fox, J. F., van Landingham, C., Subramaniam, R. (2008). Sensitivity analysis of biologically motivated model for formaldehyde-induced respiratory cancer in humans. Ann Occup Hyg, 52, 481–95.

Crump, K. S., Chen, C., Fox, J. F., Subramaniam, R., van Landingham, C. (2009). Reply. Ann Occup Hyg, 53,184–9.

Dalbey, W. E. (1982). Formaldehyde and tumors in hamster respiratory tract. Toxicology, 24, 9-14.

Dallas, C. E., Scott, M. J., Ward, J. B., Jr., Theiss, J. C. (1992). Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. J Appl Toxicol, 12, 199-203.

Dalton, P. (2003). Upper airway irritation, odor perception and health risk due to airborne chemicals. Toxicol Lett, 140-141, 239-48.

DECOS (Dutch Expert Committee on Occupational Standards) (2003). Formaldehyde. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands.

DeSesso, J. M. (1993). The relevance to humans of animal models for inhalation studies of cancer in the nose and upper airways. Quality Assurance Good Practice Regulation Law, 2, 213-31

DFG [Deutsche Forschungsgemeinschaft] (2000). Formaldehyde, in: Occupational Toxicants. The MAK Collection for Occupational Health and Safety. Weinheim: Wiley-VCH.

DFG [Deutsche Forschungsgemeinschaft] (2002). Formaldehyde, in: Occupational Toxicants, Vol 17, 163-201. Weinheim: Wiley-VCH. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics

ED_014350_00001020-00059

DFG [Deutsche Forschungsgemeinschaft] (2014). Formaldehyde [MAK Value Documentation, 2010]. The MAK Collection for Occupational Health and Safety. 1–16.

DFG [Deutsche Forschungsgemeinschaft] (2015). List of MAK and BAT Values 2015: Maximum Concentrations and Biological Tolerance Values at the Workplace. Chapter II List of Substances. Weinheim: Wiley-VCH. http://onlinelibrary.wiley.com/book/10.1002/9783527695539

ECHA (European Chemicals Agency) (2011). CLH report, 2011. Proposal for harmonized classification and labelling, substance name: formaldehyde. CLH Report. Helsinki: Submitted 28 Sep 2011 by ANSES (on behalf of the French MSCA).

ECHA (2012). RAC (Committee for Risk Assessment) Opinion proposing harmonised classification and labelling at EU level of formaldehyde. Adopted 30 November 2012. ed. Helsinki: European Chemicals Agency (ECHA). http://echa.europa.eu/documents/10162/254a73cf-ff8d-4bf4-95d1-109f13ef0f5a

Edrissi, B., Taghizadeh, K., Moeller, B. C., Kracko, D., Doyle-Eisele, M., Swenberg, J. A., Dedon, P. C. (2013). Dosimetry of N(6)-formyllysine adducts following [(1)(3)C(2)H(2)]-formaldehyde exposures in rats. Chem Res Toxicol, 26, 1421-3.

Epstein, S. S., Arnold, E., Andrea, J., Bass, W., Bishop, Y. (1972). Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol Appl Pharmacol, 23, 288-325.

Ezratty, V., Bonay, M., Neikirch, C., Orset-Guillossou, G., Dehoux, M., Koscielny S, Cabanes, P.A., Lambtozo, J., Aubier, M. (2007). Effect of formaldehyde on asthmatic responses to inhaled allergen challenge. Environ Health Perspect 115, 210–4.

Feron, V. J., Bruyntjes, J. P., Woutersen, R. A., Immel, H. R., Appelman, L. M. (1988). Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. Cancer Lett, 39, 101-11.

Feron, V. J., Til, H. P., Woutersen, R. A. (1990). Drinking water studies of formaldehyde in Sprague-Dawley rats. Toxicol Ind Health, 6, 637-9.

Fontignie-Houbrechts, N. (1981). Genetic effects of formaldehyde in the mouse. Mutat Res, 88, 109-14.

Finland (2012). HTP-värden 2012.Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6. http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf

Garcia, G. J. M., Schroeter, J. D., Segal, R. A., Stanek, J., Foureman, G. L., Kimbell, J. S. (2009). Dosimetry of nasal uptake of water-soluble and reactive gases: A first study of interhuman variability. Inhal Toxicol, 21, 607–18.

Gelbke, H. P., Groters, S., Morfeld, P. (2014). Lowest adverse effects concentrations (LOAECs) for formaldehyde exposure. Regul Toxicol Pharmacol, 70, 340-8.

Gentry, P. R., Rodricks, J. V., Turnbull, D., Bachand, A., Van Landigham, C., Shipp, A. M., Albertini, R. J., Irons, R. (2013) Formaldehyde exposure and leukemia: critical review and reevaluation of the results from a study that

ED_014350_00001020-00060

is focus for evidence of biological plausiblility. Crit Rev Toxicol, 43, 661-670.

GESTIS database. Formaldehyde, accessed July 2015: http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx

GKV Grenzwerteverordnung, 2011. BGBl. II Nr. 429/2011. Verordnung des Bundesministers für Arbeit, Soziales und Konsumentenschutz über Grenzwerte für Arbeitsstoffe sowie über krebserzeugende und über fortpflanzungsgefährdende (reproduktionstoxische) Arbeitsstoffe. http://www.arbeitsinspektion.gv.at/NR/rdonlyres/F173280B-D4FB-44D2-8269-8DB2CB1D2078/0/GKV2011.pdf.

Golden, R. (2011). Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. Crit Rev Toxicol, 41, 672-721.

Gottschling, L. M., Beaulieu, H. J., Melvin, W. W. (1984). Monitoring of formic acid in urine of humans exposed to low levels of formaldehyde. Am Ind Hyg Assoc J, 45, 19-23.

Grafström, R. C., Fornace, A. J., Jr., Autrup, H., Lechner, J. F., Harris, C. C. (1983). Formaldehyde damage to DNA and inhibition of DNA repair in human bronchial cells. Science, 220, 216-8.

Grafström, R. C., Fornace, A., Jr., Harris, C. C. (1984). Repair of DNA damage caused by formaldehyde in human cells. Cancer Res, 44, 4323-7.

Greenberg, M. I., Curtis, J. A., Vearrier, D. (2013). The perception of odor is not a surrogate marker for chemical exposure: a review of factors influencing human odor perception. Clin Toxicol (Phila), 51, 70-6.

Hansen, J., Olsen, J. H. (1995). Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control, 6, 354-60.

Hartwig, A. (ed.) (2014). Formaldehyde. In: The MAK Collection for Occupational Health and Safety, Part I, MAK Value Documentations, 1–16. Weinheim: Wiley-VCH. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics

Hauptmann, M., Lubin, J. H., Stewart, P. A., Hayes, R. B., Blair, A. (2003). Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. J Natl Cancer Inst, 95, 1615-23.

Hauptmann, M., Lubin, J. H., Stewart, P. A., Hayes, R. B., Blair, A. (2004). Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol, 159, 1117-30.

Hauptmann, M., Stewart, P. A., Lubin, J. H., Beane Freeman, L. E., Hornung, R. W., Herrick, R. F., Hoover, R. N., Fraumeni, J. F., Jr., Blair, A., Hayes, R. B. (2009). Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst, 101, 1696-708.

Hayes, R. B., Blair, A., Stewart, P. A., Herrick, R. F., Mahar, H. (1990). Mortality of U.S. embalmers and funeral directors. Am J Ind Med, 18, 641-52.

He, J. L.; Jin, L. F., Jin, H.-Y. (1998). Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. Biomed Environ Sci, 11, 87-92.

Heck, H D'A., Casanova-Schmitz, M. (1984). Biochemical toxicology of formaldehyde. Rev Biochem Toxicol, 6, 155-89.

Heck H. D'A, C. M., Casanova, M. (1995). Nasal dosimetry of formaldehyde: modeling site specificity and the effects of preexposure. Nasal toxicity and dosimetry of inhaled xenobiotics: Implications for human health. Washington DC, USA: Taylor & Francis.

Heck, H., Casanova, M. (2004). The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. Regul Toxicol Pharmacol, 40, 92-106.

Hedberg, J.J., Backlund, M., Strömberg, P., Lönn, S., Dahl, M.-L., Ingelman-Sundberg, M., Höög, J.-O. (2001). Functional polymorphism in the alcohol dehydrogenase 3 (ADH3) promoter. Pharmacogenetics, 11, 815-24.

Hermann, R. (1997). Karzinogenese der Nasenschleimhaut durch N-Nitrosodimethylamin - Inhalation bei der Ratte. Inaugural-Dissertation, Univ. Heidelberg, DE

Herskowitz H. (1950). The differential induction of lethal mutations by formalin in the two sexes of Drosophila. Science, 112, 302-3.

Herskowitz H. (1953). Formaldehyde-induced mutation in mature spermatozoa and early develop-mental stages of Drosophila melanogaster. Genetics, 38, 668-9.

Hildesheim, A., Dosemeci, M., Chan, C. C., Chen, C. J., Cheng, Y. J., Hsu, M. M., Chen, I. H., Mittl, B. F., Sun, B., Levine, P. H., Chen, J. Y., Brinton, L. A., Yang, C. S. (2001). Occupational exposure to wood, formaldehyde, and solvents and risk of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev, 10, 1145-53.

HSA (Health and Safety Authority) (2011). Code of Practice for the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No. 619 of 2001), Ireland.

HS (Health and Safety New Zealand) (2013). Workplace Exposure Standards and Biological Exposure Indices Effective from February 2013 7th Edition. The Ministry of Business, Innovation and Employment. New Zealand. http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf

HSE-MDHS 78 (1994) Methods for the determination of hazardous substances Health and safety laboratory 1994 (as cited in Affset (2008))

HSE-MDHS 102 (2010) Methods for the determination of hazardous substances health and safety laboratory. May 2010. Aldehydes in air laboratory method using high performance liquid chromatography. http://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs102.pdf. Accessed 04.26.2016HSE Health and Safety Executive. 2011. EH40 (Second edition, published 2011). http://www.hse.gov.uk/pUbns/priced/eh40.pdf

HSE (Health and Safety Executive) (2011) EH40 (Second edition, published 2011). United Kingdom. http://www.hse.gov.uk/pUbns/priced/eh40.pdf

Hubal, E. A., Schlosser, P. M., Conolly, R. B., Kimbell, J. S. (1997). Comparison of inhaled formaldehyde dosimetry predictions with DNA-protein cross-link measurements in the rat nasal passages. Toxicol Appl Pharmacol, 143, 47-55.

ED_014350_00001020-00062

Hungary (2000). 25/2000. (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról. http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM

IARC (International Agency for Research on Cancer) (1982). Formaldehyde. 29, 345-69. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon: IARC.

IARC (International Agency for Research on Cancer) (1995). Formaldehyde. 62, 217-374. Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans. Lyon: IARC.

IARC (International Agency for Research on Cancer) (2006). Formaldehyde. 88, 37-326. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon: IARC.

IARC (International Agency for Research on Cancer) (2012). Formaldehyde. 100F, 401-435. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon: IARC.

IHS (2012) Chemical Economics Handbook, Formaldehyde. https://www.ihs.com/products/formaldehyde-chemical-economics-handbook.html

INRS Metropol 001/V01 (2005) Cette méthode décrit le prélèvement en mode Actif sur cartouche de silice imprégnée et l'analyse par HPLC détection UV de la (des) substance(s) : Formaldéhyde. INRS Metropol 001/V01 (2005). http://www.inrs.fr/publications/bdd/metropol/fiche.html?refINRS=METROPOL_4. Accessed 04.26.2016

INRS (Institut National de Richerche et de Sicurite) (2012). Valeurs limites d'exposition professionnelle aux agents chimiques en France. http://www.inrs.fr/media.html?refINRS=ED%20984

INSHT [Instituto Nacional de Seguridad e Higiene en el Trabajo] (1989) Method INSHT-MTA/MA-018/A89 Determinación de formaldehído en aire - Método espectrofotométrico mediante la sal disódica del ácido 4,5-dihidroxinalftaleno 2,7-disulfónico (ácido cromotrópico). http://www.insht.es/InshtWeb/Contenidos/Documentacion/FichasTecnicas/MetodosAnalisis/Ficheros/MA/MA_018_A89.pdf. Accessed 04.26.2016

INSHT (Instituto Nacional de Seguridad e Higiene en el Trabajo) (2011). Limites de Exposicion profesional para agentes quimicos en Espana. http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_Limite/limites2011/Limites2011web.pdf

IPCS (2002) Formaldehyde. Concise International Chemical Risk Assessment Document 40. http://www.inchem.org/documents/cicads/cicads/cicad40.htm#8.6

IRSST (Institut de Recherche Robert Sauvé en santé et en sécurité du travail) (2010). How to measure formaldehyde exposure ? Canada, Québec. http://www.irsst.qc.ca/media/documents/PubScientifique/Roberge-how-to-measure-formaldehyde-exposure.pdf

ISO (2011). ISO 16000-3:2011, Indoor air -- Part 3: Determination of formaldehyde and other carbonyl compounds in indoor air and test chamber air -- Active sampling method. http://www.iso.org/iso/catalogue_detail.htm?csnumber=51812

Jakab, M. G., Klupp, T., Besenyei, K., Biro, A., Major, J., Tompa, A. (2010). Formaldehyde-induced chromosomal aberrations and apoptosis in

ED_014350_00001020-00063

peripheral blood lymphocytes of personnel working in pathology departments. Mutat Res, 698, 11-7.

Jiang, S., Yu, L., Cheng, J., Leng, S., Dai, Y., Zhang, Y., Niu, Y., Yan, H., Qu, W., Zhang, C., Zhang, K., Yang, R., Zhou, L., Zheng, Y. (2010). Genomic damages in peripheral blood lymphocytes and association with polymorphisms of three glutathione S-transferases in workers exposed to formaldehyde. Mutat Res, 695, 9-15.

JRC (Joint Research Center) (2005). HEXPOC, human exposure characterization of chemical substances; quantification of exposure routes, Authored by: Bruinen de Bruin, Y., Kotzias D. and Kephalopoulos S., EUR 21501 EN (2005)

JSOH (Japan Society for Occupational Health) (2015). Recommendation of Occupational Exposure Limits (2014–2015). The Japan Society for Occupational Health. J Occup Health, 2014; 56: 401–420.

Just, W., J Zeller, J., C Riegert, C., Speit G. (2011). Genetic polymorphisms in the formaldehyde dehydrogenase gene and their biological significance. Toxicol Letters, 207, 121–7.

Kamata, E., Nakadate, M., Uchida, O., Ogawa, Y., Suzuki, S., Kaneko, T., Saito, M. & Kurokawa, Y. (1997). Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. J Toxicol Sci, 22, 239-54.

Ke, Y.J., Qin, X.D., Zjang, Y.C., Li, H., Li, R., Yuan X., Ding, S.M. (2014) In vitro study on cytotoxicity and intracellular formaldehyde concentratioin changes after exposure to formaldehyde and its derivatives. Hum Exp Tpxicol, 33, 822-830

Kerns, W. D., Pavkov, K. L., Donofrio, D. J., Gralla, E. J., Swenberg, J. A. (1983). Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res, 43, 4382-92.

Kimbell, J. S., Overton, J. H., Subramaniam, R. P., Schlosser, P. M., Morgan, K. T., Conolly, R. B., Miller, F. J. (2001a). Dosimetry modeling of inhaled formaldehyde: binning nasal flux predictions for quantitative risk assessment. Toxicol Sci, 64, 111-21.

Kimbell, J. S., Subramaniam, R. P., Gross, E. A., Schlosser, P. M., Morgan, K. T. (2001b). Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. Toxicol Sci, 64, 100-10.

Kleinnijenhuis, A. J., Staal, Y. C., Duistermaat, E., Engel, R., Woutersen, R. A. (2013). The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure. Food Chem Toxicol, 52, 105-12.

Knasmueller, S., Holland, N., Wultsch, G., Jandl, B., Burgaz, S., Misik, M., Nersesyan, A. (2011). Use of nasal cells in micronucleus assays and other genotoxicity studies. Mutagenesis, 26, 231-8.

Kuck M., 1993, Formaldehyde. Method 3. In: Kettrup A., Angerer J., Henschler D. (Eds.) Analyses of Hazardous Substances in Air, Vol. 2, 109-119. VCH, Weinheim, http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am5000e0002a/pdf

Kuehner, S., Schlaier, M., Schwarz, K.,, Speit, G. (2012). Analysis of Leukemia-Specific Aneuploidies in Cultured Myeloid Progenitor Cells in the Absence and Presence of Formaldehyde Exposure. Toxicol Sci 128, 72-8.

ED_014350_00001020-00064

Kuehner, S., Holzmann, K., Speit, G. (2013). Characterization of formaldehyde's genotoxic mode of action by gene expression analysis in TK6 cells. Arch Toxicol, DOI 10.1007/s00204-013-1060-2.

Kuper, C. F., Oostrum, L., Ma-Hock, L., Durrer, S., Woutersen, R. A. (2009). Hyperplasia of the lymphoepithelium of NALT in rats but not in mice upon 28-day exposure to 15 ppm formaldehyde vapor. Exp Toxicol Pathol, doi:10.1016/j.etp.2009.09.004.

Ladeira, C., Viegas, S., Carolino, E., Prista, J., Gomes, M. C., Brito, M. (2011). Genotoxicity biomarkers in occupational exposure to formaldehyde--the case of histopathology laboratories. Mutat Res, 721, 15-20.

Ladeira, C., Viegas, S., Carolino, E., Gomes, M. C., Brito, M. (2013). The influence of genetic Polymorphisms in XRCC3 and ADH5 genes on the frequency of genotoxicity biomarkers in workers exposed to formaldehyde. Environ Molec Mutag, 54, 213-21.

Lam, C. W., Casanova, M., Heck, H. D. (1985). Depletion of nasal mucosal glutathione by acrolein and enhancement of formaldehyde-induced DNA-protein cross-linking by simultaneous exposure to acrolein. Arch Toxicol, 58, 67-71.

Lang, I., Bruckner, T., Triebig, G. (2008). Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regul Toxicol Pharmacol, 50, 23-36.

Lemiere, C., Desjardins, A., Cloutier, Y., Drolet, D., Perrault, G., Cartier, A., Malo, J. L. (1995). Occupational asthma due to formaldehyde resin dust with and without reaction to formaldehyde gas. Eur Respir J, 8, 861-5.

Liber, H. L., Benforado, K., Crosby, R. M., Simpson, D., Skopek, T. R. (1989). Formaldehyde-induced and spontaneous alterations in human hprt DNA sequence and mRNA expression. Mutat Res, 226, 31-7.

Lin, D., Guo, Y., Yi, J., Kuang, D., Li, X., Deng, H., Huang, K., Guan, L., He, Y., Zhang, X., Hu, D., Zhang, Z., Zheng, H., Zhang, X., McHale, C.M., Zhang, L., Wu, T (2013). Occupational Exposure to Formaldehyde and Genetic Damage in the Peripheral Blood Lymphocytes of Plywood Workers. J Occup Health, 55, 284-91.

Lu, K., Ye, W., Gold, A., Ball, L. M., Swenberg , J. A. (2009). Formation of S-[1-(N2-Deoxyguanosinyl)methyl]glutathione between Glutathione and DNA Induced by Formaldehyde. J Am Chem Soc, 131, 3414–5.

Lu, K., Collins, L. B., Ru, H., Bermudez, E., Swenberg, J. A. (2010a). Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. Toxicol Sci, 116, 441-51.

Lu, K., Ye, W., Zhou, L., Collins, L. B., Chen, X., Gold, A., Ball., L. M., Swenberg, J. A. (2010b). Structural characterization of formaldehyde-induced cross-links between amino acids and deoxynocleosides and their oligomers. J Am Chem Soc, 132, 3388-99.

Lu, K., Moeller, B., Doyle-Eisele, M., Mcdonald, J., Swenberg, J. A. (2011). Molecular dosimetry of N2-hydroxymethyl-dG DNA adducts in rats exposed to formaldehyde. Chem Res Toxicol, 24, 159-61.

Lu, K., Craft, S., Nakamura, J., Moeller, B. C., Swenberg, J. A. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine. Chem Res Toxicol, 25, 664-75.

ED_014350_00001020-00065

Magana-Schwencke, N., Moustacchi, E. (1980). Biochemical analysis of damage induced in yeast by formaldehyde. Mutat Res, 70, 29-35.

Marsh, G. M., Youk, A. O., Buchanich, J. M., Cassidy, L. D., Lucas, L. J., Esmen, N. A., Gathuru, I. M. (2002). Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde. Toxicol Ind Health, 18, 257-68.

Marsh, G. M., Youk, A. O. (2004). Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. Regul Toxicol Pharmacol, 40, 113-24.

Marsh, G. M., Youk, A. O. (2005). Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute. Regul Toxicol Pharmacol, 42, 275-83.

Marsh, G. M., Youk, A. O., Buchanich, J. M., Erdal, S., Esmen, N. A. (2007a). Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers. Regul Toxicol Pharmacol, 48, 308-19.

Marsh, G. M., Youk, A. O., Morfeld, P. (2007b). Mis-specified and non-robust mortality risk models for nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study. Regul Toxicol Pharmacol, 47, 59-67.

Marsh, G. M., Morfeld, P., Collins, J. J., Symons, J. M. (2014). Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. J Occup Med Toxicol, 9, 22.

McGregor, D., Bolt, H., Cogliano, V., Richter-Reichhelm, H. B. (2006). Formaldehyde and glutaraldehyde and nasal cytotoxicity: case study within the context of the 2006 IPCS human framework for the analysis of a cancer mode of action for humans. Crit Rev Toxicol, 36, 821-35.

McGwin, G., Lienert, J., Kennedy, J. I. (2010). Formaldehyde exposure and asthma in children: a systematic review. Environ Health Perspect, 118, 313-7.

Meng, F., Bermudez, E., McKinzie, P.B., Andersen, M.E., Clewell, H.J., Parsons, B.L. (2010). Measurement of tumor-associated mutations in the nasal mucosa of rats exposed to varying doses of formaldehyde. Reg Toxicol Pharmacol, 57, 274-83.

Merk, O., Speit, G. (1998). Significance of formaldehyde-induced DNA-protein crosslinks for mutagenesis. Environ Mol Mutagen, 32, 260-8.

Meyers, A. R., Pinkerton, L. E., Hein, M. J. (2013). Cohort mortality study of garment industry workers exposed to formaldehyde: update and internal comparisons. Am J Ind Med, 56, 1027-39.

Migliore, L., Ventura, L., Barale, R., Loprieno, N., Castellino, S., Pulci, R. (1989). Micronuclei and nuclear anomalies induced in the gastro-intestinal epithelium of rats treated with formaldehyde. Mutagenesis, 4, 327-34.

Moeller, B. C., Lu, K., Doyle-Eisele, M., Mcdonald, J., Gigliotti, A., Swenberg, J. A. (2011). Determination of N2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chem Res Toxicol, 24, 162-4.

Monticello, T. M., Swenberg, J. A., Gross, E. A., Leininger, J. R., Kimbell, J. S., Seilkop, S., Starr, T. B., Gibson, J. E., Morgan, K. T. (1996). Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. Cancer Res, 56, 1012-22.

ED_014350_00001020-00066

Monticello, T. M., Morgan, K. T. (1997). Chemically-induced nasal carcinogenesis and epithelial cell proliferation : a brief review. Mut Res, 380, 33-41

Morfeld, P. (2013). Formaldehyde and leukemia: missing evidence! Cancer Causes Control, 24, 203-4.

Morgan, K. T., Patterson, D. L., Gross, E. A. (1986). Responses of the nasal mucociliary apparatus of F-344 rats to formaldehyde gas. Toxicol Appl Pharmacol, 82, 1-13.

Mueller, J. U., Bruckner, T., Triebig, G. (2013). Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int Arch Occup Environ Health, 86, 107-17.

Natarajan, A. T., Darroudi, F., Bussman, C. J., Van Kesteren-Van Leeuwen, A. C. (1983). Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays in vivo and vitro. Mutat Res, 122, 355-60.

NED (2007). Limit values The Netherlands: Dutch Legal Public Limit Values (Nationale wettelijke publieke grenswaarden). Dutch Law on Labour conditions. http://www.ser.nl/nl/themas/grenswaarden/procedure%20tot%202007.aspx

NEG (Nordic Expert Group) (2003). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards, 132. Formaldehyde.

Neuss, S., Speit, G. (2008). Further characterization of the genotoxicity of formaldehyde in vitro by the sister chromatid exchange test and co-cultivation experiments. Mutagenesis, 23, 355-7.

Neuss, S., Moepps, B., Speit, G. (2010a). Exposure of human nasal epithelial cells to formaldehyde does not lead to DNA damage in lymphocytes after co-cultivation. Mutagenesis, doi:10.1093/mutage/geq013

Neuss, S., Holzmann, K., Speit, G. (2010b). Gene expression changes in primary human nasal epithelial cells exposed to formaldehyde in vitro. Toxicol Lett, 198, 289–95.

Nielsen, G. D., Hougaard, K. S., Larsen, S. T., Hammer, M., Wolkoff, P., Clausen, P. A., Wilkins, C. K., Alarie, Y. (1999). Acute airway effects of formaldehyde and ozone in BALB/c mice. Hum Exp Toxicol, 18, 400-9.

Nielsen, G. D., Wolkoff, P. (2010). Cancer effects of formaldehyde: a proposal for an indoor air guideline value. Arch Toxicol, 84, 423-46.

Nielsen, G. D., Larsen, S. T., Wolkoff, P. (2013). Recent trend in risk assessment of formaldehyde exposures from indoor air. Arch Toxicol, 87, 73–98.

Nimmermark, S. (2004). Odour influence on well-being and health with specific focus on animal production emissions. Ann Agric Environ Med, 11, 163-73.

NIOSH (1994a). NIOSH Method 2541, Formaldehyde by GC: In: Eller, P. M., Cassinelli, M. E. (eds.) NIOSH Manual of Analytical Methods, 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 94-113. http://www.cdc.gov/niosh/docs/2003-154/pdfs/2541.pdf

NIOSH (1994b). Formaldehyde by VIS: Method 3500. In: Eller, P. M., Cassinelli, M. E. (eds.) NIOSH Manual of Analytical Methods, 4th ed. Cincinnati, OH:

U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Ocupational Safety and Health. DHHS (NIOSH) Publication No. 94-113.

NIOSH (2003). NIOSH Method: 2016, Formaldehyde. Issue 2 Evaluation: Full Issue 1: 15 January 1998; Issue 2: 15 March 2003, NIOSH Manual of Analytical Methods (NMAM), Fourth Edition http://www.cdc.gov/niosh/docs/2003-154/pdfs/2016.pdf

NIOSH (2007). Pocket guide to chemical hazards. Department of Health and Human Services. Centers for Disease Control and Prevention National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2005-149/pdfs/2005-149.pdf

Norway (2011). Administrative normer for forurensning i arbeidsatmosfære. http://www.arbeidstilsynet.no/binfil/download2.php?tid=77907

NTP (National Toxicology Program) (2010). "Final report on carcinogens background document for formaldehyde." Rep Carcinog Backgr Doc: i-512. https://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/november/formaldehyde_bd_final.pdf

NRC (National Research Council of the National Academies) (2014). Review of the formaldehyde assessment in the National Toxicology Program. 12th Report on Carcinogens. The National Academies Press, Washington, 2014. ISBN-13: 978-0-309-31227-1.

Odeigah, P. G. (1997). Sperm head abnormalities and dominant lethal effects of formaldehyde in albino rats. Mutat Res, 389, 141-8.

Olsen, J. H., Jensen, S. P., Hink, M., Faurbo, K., Breum, N. O., Jensen, O. M. (1984). Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer, 34, 639-44.

Ontario Ministry of Labour (2013). Current Occupational Exposure Limits for Ontario workplaces Required under Regulation 833. http://www.labour.gov.on.ca/english/hs/pdf/ontario_oels.pdf

Orsière, T., Sari-Minodier, I., Iarmarcovai, G., Botta, A. (2006). Genotoxic risk assessment of pathology and anatomy laboratory workers exposed to formaldehyde by use of personal air sampling and analysis of DNA damage in peripheral lymphocytes. Mut Res, 60, 30–41.

OSHA (1985). Formaldehyde: Method 52. In: OSHA Analytical Methods Manual, Salt Lake City, UT: U.S. Department of Labor, Occupational Safety and Health Administration, OSHA Analytical Laboratory. http://www.cdc.gov/niosh/docs/2003-154/pdfs/3500.pdf

OSHA [Occupational Safety and Health Administration] (1989) Sampling and analytical methods for Acrolein and/or Formaldehyde OSHA-52 https://www.osha.gov/dts/sltc/methods/organic/org052/org052.html. Accessed 04.27.2016

OSHA [Occupational Safety and Health Administration] (1990) Sampling and analytical methods for formaldehyde in workplace atmospheres (3m model 3721 monitor) method ID-205 https://www.osha.gov/dts/sltc/methods/inorganic/id205/id205.html. Accessed 04.26.2016

OSHA (2005). OSHA Method no: 1007, Formaldehyde (Diffusive Samplers) Control no.: T-1007-FV-01-0505-M, Methods Development Team, Industrial Hygiene Chemistry Division, OSHA Salt Lake Technical Center Sandy, UT

ED_014350_00001020-00068

84070-6406
https://www.osha.gov/dts/sltc/methods/mdt/mdt1007/1007.pdf

OSHA(2006). Occupational Safety and Health Administration (OSHA) (2006) Air Contaminants.
https://www.osha.gov/dsg/annotated-pels/tablez-1.html

Pala, M., Ugolini, D., Ceppi, M., Rizzo, F.; Maiorana, L., Bolognesi, C., Schiliro, T., Gilli, G., Bigatti, P., Bono, R., Vecchio, D. (2008). Occupational exposure to formaldehyde and biological monitoring of research institute workers. Cancer Detect Prevent, 32, 121-26.

Paustenbach, D., Alarie, Y., Kulle, T., Schachter, N., Smith, R., Swenberg, J., Witschi, H., Horowitz, S. B. (1997). A recommended occupational exposure limit for formaldehyde based on irritation. J Toxicol Environ Health, 50, 217-63.

Peteffi, G.P., Basso, D.A. Silva, L., Antunes, M.V., Wilhelm, C., Valandro, E.T., Glaeser, J., Kaefer, D., Linden, R. (2015) Evaluation of genotoxicity in workers exposed to low levels of formaldehyde in a furniture manufacturing facility. Toxicol Ind Health. Toxicol Ind Health. 2015 May 13. pii: 0748233715584250. *[Epub ahead of print]*

Peteffi, G.P., Antunes, M.V., Carrer, C., Valandro, E.T., Santos, S., Glaeser, J., Mattos, L., Da Silva, L.B., Linden, R. (2016) Environmental and biological monitoring of occupational formaldehyde exposure resulting from the use of products for hair straightening. Environ Sci Pollut Res Int. 23(1):908-17.

Pinkerton, L. E., Hein, M. J., Stayner, L. T. (2004). Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med, 61, 193-200.

Pira, E., Romano, C., Verga, F., La Vecchia, C. (2014). Mortality from lymphohematopoietic neoplasms and other causes in a cohort of laminated plastic workers exposed to formaldehyde. Cancer Causes Control, 25, 1343-9.

Poland (2002). The Ordinance of the Minister of Labour and Social Policy on the Maximum Admissible Concentrations and Intensities of Harmful to Health Agents in the Working Environment. Rozporzñdzenie ministra pracy i polityki spo¸ecznej Z dnia 29 listopada 2002 r.
http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/legaldocument/wcms_151572.pdf

Rager, J. E., Moeller, B. C., Miller, S. K., Kracko, D., Doyle-Eisele, M., Swenberg, J. A., Fry, R. C. (2014). Formaldehyde-associated changes in microRNAs: tissue and temporal specificity in the rat nose, white blood cells, and bone marrow. Toxicol Sci, 138, 36-46.

Rasmuson, A., Larsson, J. (1992). Somatic and germline mutagenesis assayed by the unstable zeste-white test in Drosophila melanogaster. Mutagenesis, 7, 219-23.

Recio L. (1997) Oncogene and tumor suppressor gene alterations in nasal tumors. Mutat Res. 380(1-2): 27-31.

Recio, L., Sisk, S., Pluta, L., Bermudez, E., Gross, E. A., Chen, Z., Morgan, K., Walker, C. (1992). p53 mutations in formaldehyde-induced nasal squamous cell carcinomas in rats. Cancer Res, 52, 6113-6.

Reuss, G. D. W., Grundler, O., Holt, A. (1988). Formaldehyde. In: Ullmann's Encyclopedia of Industrial Chemistry, Weinheim, VCH Publishers.

ED_014350_00001020-00069

Rhomberg, L. R., Bailey, L. A., Goodman, J. E., Hamade, A. K., Mayfield, D. (2011). Is exposure to formaldehyde in air causally associated with leukemia?--A hypothesis-based weight-of-evidence analysis. Crit Rev Toxicol, 41, 555-621.

Roush, G. C., Walrath, J., Stayner, L. T., Kaplan, S. A., Flannery, J. T., Blair, A. (1987). Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. J Natl Cancer Inst, 79, 1221-4.

Rusch Gm, B. H., Rinehart W.E. (1983a). A 26-week inhalation toxicity study with formaldehyde in the monkey, rat and hamster. In: Je, G. (ed.) Formaldehyde Toxicity. New York: Hemisphere.

Rusch, G. M., Clary, J. J., Rinehart, W. E., Bolte, H. F. (1983b). A 26-week inhalation toxicity study with formaldehyde in the monkey, rat, and hamster. Toxicol Appl Pharmacol, 68, 329-43.

Safe Work Australia (2011). Workplace exposure standards for airborne contaminants date of effect: 22 december 2011. http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace_Exposure_Standards_for_Airborne_Contaminants.pdf

Salthammer, T. (2010) Formaldehyde in the indoor environment. Chem Rev. 2010, 110, 2536-2572.

Santovito, A., Schiliro, T., Castellano, S., Cervella, P., Bigatti, M. P., Gilli, G., Bono, R., Delpero, M. (2011). Combined analysis of chromosomal aberrations and glutathione S-transferase M1 and T1 polymorphisms in pathologists occupationally exposed to formaldehyde. Arch Toxicol, 85, 1295-302.

Santovito, A., Cervella, P., Delpero, M. (2014). Chromosomal damage in peripheral blood lymphocytes from nurses occupationally exposed to chemicals. Hum Exp Toxicol, 33, 897-903.

Sax, S. N., Benett, D.H. (2004). Differences in source emission rates of volatile organic compounds in inner-city residences of New York City and Los Angeles. J Expo Anal Environ Epidemiol 14(1): S95-109.

Schaper, M. (1993). Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J, 54, 488-544.

Schmid, E., Göggelmann, W., Bauchinger, M. (1986). Formaldehyde-induced cytotoxic, genotoxic and mutagenic response in human lymphocytes and Salmonella typhimurium. Mutagenesis, 1, 427-31.

Schmid, O., Speit, G. (2007). Genotoxic effects induced by formaldehyde in human blood and implications for the interpretation of biomonitoring studies. Mutagenesis, 22, 69-74.

Schmitz P., Tschickardt M., (2002). Aldehydes (Formaldehyde, Acetaldehyde, Propionaldehyde, Butyraldehyde, Glutaraldehyde, Pentanal, Hexanal, Heptanal, Octanal, Nonanal). Method 2. In: Kettrup A, Angerer J, Greim H (Eds.) Analyses of Hazardous Substances in Air, Vol. 5, 3-13. Weinheim: Wiley-VCH. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am5000e0005/pdf

Schwilk, E., Zhang, L., Smith, M. T., Smith, A. H., Steinmaus, C. (2010). Formaldehyde and leukemia: an updated meta-analysis and evaluation of bias. J Occup Environ Med, 52, 878-86.

ED_014350_00001020-00070

SCOEL (Scientific Committee on Occupational Exposure Limits) SCOEL/SUM/125 (2008). March 2008

SCOEL (Scientific Committee on Occupational Exposure Limits) (2013). Methodology for the derivation of occupational exposure limits; key documentation (version 7) June 2013

Sexton, K., Adgate, J.L. (2004). Comparison of personal, indoor, and outdoor exposures to hazardous air pollutants in three urban communities. Environ Sci Technol 38(2): 423-430.

Shaham, J., Bomstein, Y., Meltzer, A., Kaufman, Z., Palma, E., Ribak, J. (1996). DNA-protein crosslinks, a biomarker of exposure to formaldehyde--in vitro and in vivo studies. Carcinogenesis, 17, 121-5.

Shaham, J., Bomstein, Y., Melzer, A., Ribak, J. (1997). DNA-protein crosslinks and sister chromatid exchenes as biomarkers of exposure to formaldehyde. Int J Occuo Environ Health, 3, 95-104.

Shaham, J., Gurvich, R., Kaufman, Z. 2002. Sister chromatid exchange in pathology staff workers occupationally exposed to formaldehyde. Mut Res, 514, 515-23.

Shaham, J., Bomstein, Y., Gurvich, R., Rashkovsky, M., Kaufman, Z. (2003). DNA-protein crosslinks and p53 protein expression in relation to occupational exposure to formaldehyde. Occup Environ Med, 60, 403-9.

Shusterman, D. (2001). Odor-associated health complaints: competing explanatory models. Chem Senses, 26, 339-43.

Shusterman, D., Lipscomb, J., Neutra, R., Satin, K. (1991). Symptom prevalence and odor-worry interaction near hazardous waste sites. Environ Health Perspect, 94, 25-30.

Siew, S. S., Kauppinen, T., Kyyronen, P., Heikkila, P., Pukkala, E. (2012). Occupational exposure to wood dust and formaldehyde and risk of nasal, nasopharyngeal, and lung cancer among Finnish men. Cancer Manag Res, 4, 223-32.

Soffritti, M., Maltoni, C., Maffei, F., Biagi, R. (1989). Formaldehyde: an experimental multipotential carcinogen. Toxicol Ind Health, 5, 699-730.

Soffritti, M., Belpoggi, F., Lambertin, L., Lauriola, M., Padovani, M., Maltoni, C. (2002). Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. Ann N Y Acad Sci, 982, 87-105.

Speit, G., Schmid, O. (2006). Local genotoxic effects of formaldehyde in humans measured by the micronucleus test with exfoliated epithelial cells. Mut Res, 613, 1-9.

Speit, G., Schütz, P., Högel, J., Schmid, O. (2007). Characterization of the genotoxic potential of formaldehyde in V79 cells. Mutagenesis 22: 387-394.

Speit, G., Schmid, O., Fröhlich-Keller, M., Lang, I, Triebig, G. (2007a). Assessment of local genotoxic effects of formaldehyde in humans measured by the micronucleus test with exfoliated buccal mucosa cells. Mut Res, 627, 129-135.

Speit, G., Zeller, J., Schmid, O., Elhajouji, A., Ma-Hock, L., Neuss, S. (2009). Inhalation of formaldehyde does not induce systemic genotoxic effects in rats. Mut Res, 677, 76–85.

ED_014350_00001020-00071

Speit, G., Neuss, S., Schmid, O. (2010). The human lung cell line A549 does not develop adaptive protection against the DNA-damaging action of formaldehyde. Environ Mol Mutagen, 51, 130–7.

Speit, G., Schütz, P., Weber, I., Ma-Hock, L., Kaufmann, W., Gelbke, H.P., Durrer, S. (2011a). Analysis of micronuclei, histopathological changes and cell proliferation in nasal epithelium cells of rats after exposure to formaldehyde by inhalation. Mut Res, 721, 127-35.

Speit, G., Kühner, S., Linsenmeyer, R.,, Schütz, P. (2011b). Does formaldehyde induce aneuploidy? Mutagenesis, doi:10.1093/mutage/ger050

Speit, G., Ladeira, C., Linsenmeyer, R., Schutz, P., Hogel, J. (2012a). Re-evaluation of a reported increased micronucleus frequency in lymphocytes of workers occupationally exposed to formaldehyde. Mutat Res, 744, 161-6.

Speit, G., Linsenmeyer, R., Schütz, P, Kuehner, S, (2012b). Insensitivity of the in vitro cytokinesis-block micronucleus assay with human lymphocytes for the detection of DNA damage present at the start of the cell culture. Mutagenesis, 27, 743-7.

Speit, G. (2013a). Does the recommended lymphocyte cytogenesis-block micronucleus assay for human biomonitoring actually detect DNA damage induced by occupational and environmental exposure to genotoxic chemicals? Mutagenesis DOI: 10.1093/mutage/get026

Speit, G. (2013b). RESPONSE - RE: Insensitivity of the in vitro cytokinesis-block micronucleus assay with human lymphocytes for the detection of DNA damage present at the start of the cell culture (Mutagenesis, 27, 743–747, 2012). Mutagenesis, 28, 371–4.

Speit, G., Linsenmeyer, R., Duong, G., Bausinger, J. (2014). Investigations on potential co-mutagenic effects of formaldehyde. Mutat Res, 760, 48-56.

SRI (2009). CEH Marketing Research Report, as cited in: http://www.formacare.org/about-formaldehyde/eu-market/

Starr, T. B., Swenberg, J. A. (2013). A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. Reg Toxicol Pharmacol, 65, 311–15.

Subramaniam, R. P., Crump, K. S., van Landingham, C., White, P., Chen, C., Schlosser, P. M. (2007). Uncertainties in the CIIT model for formaldehyde-induced carcinogenicity in the rat: a limited sensitivity analysis-I. Risk Anal, 27, 1237–53.

Subramaniam, R. P., Chen, C., Crump, K. S., de Voney, D., Fox, J. F., Portier, C. J., Schlosser, P. M., Thompson, C. M., White, P. (2008). Uncertainties in biologically-based modelling of formaldehyde-induced respiratory cancer risk: identification of key issues. Risk Anal, 28, 907–21.

Suruda, A., Schulte, P., Boeninger, M., Hayes, R., Livingston, G.K., Steenland, K., Stewart, P., Herrick, H., Douthit, D., Fingerhut, M.A. (1993). Cytogenetic effects of formaldehyde in student of mortuary science. Cancer Epidemiol Biomarkers Prev, 2, 453-60

SUVA (Schweizerische Unfallversicherungsanstalt) (2015). Grenzwerte am Arbeitsplatz 2015. MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen. https://extra.suva.ch/suva/b2c/b2c/start.do;jsessionid=1SNHbj-0PppElAFvO7Ks0eUouc2-TQFykRoe_SAPdq5f-GW926vKwRXNGAkQrfkO;saplb_*=(J2EE505057620)505057650

SWEA (Swedish Work Environment Authority) (2011). The Swedish Work Environment Authority's provisions and general recommendations on occupational exposure limit values. http://www.av.se/dokument/inenglish/legislations/eng1118.pdf

Swenberg, J. A., Kerns, W. D., Mitchell, R. I., Gralla, E. J., Pavkov, K. L. (1980). Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res, 40, 3398-402.

Swenberg, J. A., Lu, K., Moeller, B. C., Gao, L., Upton, P. B., Nakamura, J., Starr, T. B. (2011). Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment. Toxicol Sci, 120, 130–45.

Swenberg, J. A., Moeller, B. C., Lu, K., Rager, J. E., Fry, R. C., Starr, T. B. (2013). Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment. Toxicol Pathol, 41, 181-9.

Szabad, J., Soos, I., Polgar, G., Hejja, G. (1983). Testing the mutagenicity of malondialdehyde and formaldehyde by the Drosophila mosaic and the sex-linked recessive lethal tests. Mutat Res, 113, 117-33.

Tang, X., Y. (2009). Formaldehyde in China: production, consumption, exposure levels, and health effects. Environ Int 35(8): 1210-1224.

Thomson, E. J., Shackleton, S., Harrington, J. M. (1984). Chromosome aberrations and sister-chromatid exchange frequencies in pathology staff occupationally exposed to formaldehyde. Mutat Res, 141, 89-93.

Til, H. P., Woutersen, R. A., Feron, V. J., Hollanders, V. H., Falke, H. E., Clary, J. J. (1989). Two-year drinking-water study of formaldehyde in rats. Food Chem Toxicol, 27, 77-87.

Tobe, M., Naito, K., Kurokawa, Y. (1989). Chronic toxicity study on formaldehyde administered orally to rats. Toxicology, 56, 79-86.

Uotila, L., Koivusalo, M. (1987). Multiple forms of formaldehyde dehydrogenase from human red blood cells. Hum Hered, 37, 102-6.

US EPA (US Environmental Protection Agency) (1999). Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air. Second Edition. Compendium Method TO-11A: Determination of Formaldehyde in Ambient Air Using Adsorbent Cartridge Followed by High Performance Liquid Chromatography (HPLC) [Active Sampling Methodology] http://www.epa.gov/ttnamti1/files/ambient/airtox/to-11ar.pdf

Vaughan, T. L., Strader, C., Davis, S., Daling, J. R. (1986a). Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. Int J Cancer, 38, 677-83.

Vaughan, T. L., Strader, C., Davis, S., Daling, J. R. (1986b). Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int J Cancer, 38, 685-8.

Vaughan, T. L., Stewart, P. A., Teschke, K., Lynch, C. F., Swanson, G. M., Lyon, J. L., Berwick, M. (2000). Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. Occup Environ Med, 57, 376-84.

Viegas, S., Ladeira, C., Nunes, C., Malta-Vacas, J., Gomes, M., Brito, M., Mendonca, P., Prista, J. (2010). Genotoxic effects in occupational exposure to formaldehyde: A study in anatomy and pathology laboratories and

ED_014350_00001020-00073

formaldehyde-resins production. J Occup Med Toxicol, 5, 25, http://www.occup-med.com/content/5/1/25.

Walrath, J., Fraumeni, J. F., Jr. (1983). Mortality patterns among embalmers. Int J Cancer, 31, 407-11.

Wang W., Yan, Y., Li, C.W., Xia, H.M., Chao, S.S., Wang De Y., Wang, Z.P. (2014) Live human nasal epithelial cells (hNECc) on chip for in vitro testing of gaseous formaldehyde toxicity via airway delivery. Lab Chip, 14, 677-680.

Ward, J. B., Jr., Hokanson, J. A., Smith, E. R., Chang, L. W., Pereira, M. A., Whorton, E. B., Jr., Legator, M. S. (1984). Sperm count, morphology and fluorescent body frequency in autopsy service workers exposed to formaldehyde. Mutat Res, 130, 417-24.

West, S., Hildesheim, A., Dosemeci, M. (1993). Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. Int J Cancer, 55, 722-7.

WHO (World Health Organisation) (1989). International Programme on Chemical Safety, Environmental Health Criteria 89, Formaldehyde, Geneva, World Health Organization.

WHO (World Health Organisation) (2010). WHO Guidelines for Indoor Air Quality: Selected Pollutants, Geneva, World Health Organization.

Wilhelmsson, B., Holmstrom, M. (1992). Possible mechanisms of formaldehyde-induced discomfort in the upper airways. Scand J Work Environ Health, 18, 403-7.

Wilmer, J. W., Woutersen, R. A., Appelman, L. M., Leeman, W. R., Feron, V. J. (1989). Subchronic (13-week) inhalation toxicity study of formaldehyde in male rats: 8-hour intermittent versus 8-hour continuous exposures. Toxicol Lett, 47, 287-93.

Wolf, D. C., Gross, E. A., Lyght, O., Bermudez, E., Recio, L., Morgan, K. T. (1995). Immunohistochemical localization of p53, PCNA, and TGF-alpha proteins in formaldehyde-induced rat nasal squamous cell carcinomas. Toxicol Appl Pharmacol, 132, 27-35.

Wolkoff, P. & Nielsen, G. D. 2010. Non-cancer effects of formaldehyde and relevance for setting an indoor air guideline. Environ Int, 36, 788-99.

Woutersen, R. A., Appelman, L. M., Wilmer, J. W., Falke, H. E., Feron, V. J. (1987). Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. J Appl Toxicol, 7, 43-9.

Woutersen, R. A., Van Garderen-Hoetmer, A., Bruijntjes, J. P., Zwart, A., Feron, V. J. (1989). Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. J Appl Toxicol, 9, 39-46.

Yager, J. W., Cohn, K. L., Spear, R. C., Fisher, J. M., Morse, L. (1986). Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. Mutat Res, 174, 135-9.

Ye, X., Yan, W., Xie, H., M. Zhao, M., Ying, C. (2005). Cytogenetic analysis of nasal mucosa cells and lymphocytes from high-level long-term formaldehyde exposed workers and low-level short-term exposed waiters. Mut Res, 588, 22–27.

Ye, X., Ji, Z., Wei, C., McHale, C. M., Ding, S., Thomas, R., Yang, X. Zhang, L. (2013). Inhaled formaldehyde induces DNA-protein crosslinks and oxidative

ED_014350_00001020-00074

stress in bone marrow and other distant organs of exposed mice. Environ Molec Mutag, 54,705-18.

Ying, C. J., Yan, W. S.; Zhao, M. Y., Ye, X. L., Xie, H., Yin, S. Y., Zhu X. S. (1997). Micronuclei in nasal mucosa, oral mucosa and lymphocytes in students exposed to formaldehyde vapor in anatomy class. Biomed Environ Sci, 10, 451-5.

Ying, C. J., Ye, X. L., Xie, H., Yan, W. S.; Zhao, M. Y., Xia, T. & Yin, S. Y. 1999. Lymphocyte subsets and sister-chromatid exchanges in the students exposed to formaldehyde vapor. Biomed Environ Sci 12, 88-94

Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W. M., Starr T. B. & Swenberg, J. A. 2015. Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicol Sci, 146, 170–82.

Zeller, J., Neuss, S., Mueller, J. U., Kuhner, S., Holzmann, K., Hogel, J., Klingmann, C., Bruckner, T., Triebig, G., Speit, G. (2011a). Assessment of genotoxic effects and changes in gene expression in humans exposed to formaldehyde by inhalation under controlled conditions. Mutagenesis, 26, 555-61.

Zeller, J., Ulrich, A., Mueller, J. U., Riegert, C., Neuss, S., Bruckner, T., Triebig, G., Speit, G. (2011b). Is individual nasal sensitivity related to cellular metabolism of formaldehyde and susceptibility towards formaldehyde-induced genotoxicity? Mutat Res, 723, 11-7.

Zeller, J., Högel, J., Linsenmeyer, R., Teller, C., Speit G. (2012). Investigations of potential susceptibility toward formaldehyde-induced genotoxicity. Arch Toxicol, 86, 1465–73

Zhang, L., Tang, X., Rothman, N., Vermeulen, R., Ji, Z., Shen, M., Qiu, C., Guo, W., Liu, S. (2010). Occupational exposure to formaldehyde, hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cell. Cancer Epidemiol Biomarkers Prev 19, 80-88

ED_014350_00001020-00075

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);

- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries
  (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm)
  or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Priced subscriptions:

- via one of the sales agents of the Publications Office of the European Union
  (http://publications.europa.eu/others/agents/index_en.htm).

ED_014350_00001020-00076

KE-05-16-063-EN-N

doi: 10.2767/399843

ISBN 978-92-79-64151-0