Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of
Formaldehyde

EC number: 200-001-8
CAS number: 50-00-0

CLH-O-0000003155-80-01/F

Adopted

30 November 2012

30 November 2012
CLH-O-0000003155-80-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE PROPOSAL FOR THE HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Chemical name: Formaldehyde

EC number: 200-001-8

CAS number: 50-00-0

The proposal was submitted by **France** and received by the RAC on **28 September 2011.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification:

	CLP	**DSD**
Current entry in Annex VI to Regulation (EC) No 1272/2008	Acute Tox. 3* – H331 Acute Tox. 3* – H311 Acute Tox. 3* – H301 Skin Corr. 1B – H314 Skin Sens. 1 – H317 Carc. 2 – H351 SCL: Skin Corr. 1B: C ≥ 25 % Skin Irrit. 2: 5 % ≤ C < 25 % Eye Irrit. 2: 5 % ≤ C < 25 % STOT SE 3: C ≥ 5 % Skin Sens. 1: C ≥ 0,2	T; R23/24/25 C; R34 R43 Carc. Cat. 3; R40 SCL: T; R23/24/25: C ≥25 % Xn; R20/21/22: 5 % ≤ C < 25 % C; R34: C ≥25 % Xi; R36/37/38: 5 % ≤ C < 25 % R43: C ≥ 0,2 %
Proposal by dossier submitter for consideration by the RAC	**Muta. 2 – H341** **Carc. 1A – H350**	**Muta. Cat. 3; R68** **Carc. Cat. 1; R45**

Resulting harmonised classification (future entry in Annex VI to Regulation (EC) No 1272/2008) as proposed by dossier submitter	Acute Tox. 3* – H331 Acute Tox. 3* – H311 Acute Tox. 3* – H301 Skin Corr. 1B – H314 Skin Sens. 1 – H317 Muta. 2 – H341 Carc. 1A – H350 SCL: Skin Corr. 1B: C ≥ 25 % Skin Irrit. 2: 5 % ≤ C < 25 % Eye Irrit. 2: 5 % ≤ C < 25 % STOT SE 3: C ≥ 5 % Skin Sens. 1: C ≥ 0,2	T; R23/24/25 R43 Muta. Cat. 3; R68 Carc. Cat. 1; R45 SCL: T; R23/24/25: C ≥25 % Xn; R20/21/22: 5 % ≤ C < 25 % C; R34: C ≥25 % Xi; R36/37/38: 5 % ≤ C < 25 % R43: C ≥ 0,2 %

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/web/guest/harmonised-classification-and-labelling-previous-consultations*** on **31 October 2011.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **15 December 2011.**

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Agnes Schulte**

Co-rapporteur, appointed by the RAC: **Boguslaw Baranski**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **30 November 2012** and the comments received are compiled in Annex 2.

The RAC opinion was adopted by a **simple majority of all members**; one RAC member expressed a minority position regarding the RAC assessment for germ cell mutagenicity. The minority position, including its grounds, was made available in a separate document which has been published at the same time as the opinion.

OPINION OF THE RAC

The RAC adopted the opinion that **Formaldehyde** should be classified and labelled as follows[1]:

1 Note that not all hazard classes have been evaluated

Classification and labelling in accordance with the CLP Regulation:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
605-001-00-5	formaldehyde …%	200-001-8	50-00-0	Carc. 1B Muta. 2 Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* Skin Corr. 1B Skin Sens. 1	H350 H341 H301 H311 H331 H314 H317	GHS08 GHS06 GHS05 Dgr	H350 H341 H301 H311 H331 H314 H317		* 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 % Skin Sens. 1; H317: C ≥ 0,2 %	B, D

Classification and labelling in accordance with the criteria of DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
605-001-00-5	formaldehyde …%	200-00-8	50-00-0	Carc. Cat. 2; R45 Muta. Cat. 3; R68 T; R23/24/25 C; R34 R43	T R: 23/24/25-34-43-45-68 S: 45-53	T; R23/24/25: C ≥ 25 % Xn; R20/21/22: 5 % ≤ C < 25 % C; R34: C ≥ 25 % Xi; R36/37/38: 5 % ≤ C < 25 % R43: C ≥ 0,2 %	B, D

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

Mutagenicity

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Positive evidence is available in vivo at the site of contact in somatic cells. The evidence consists of induction of chromosomal aberrations in broncho-alveolar cells of rats after inhalation of formaldehyde (Dallas et al., 1992) and an increased number of micronuclei in epithelial cells along the gastro-intestinal tract of rats after oral administration of formaldehyde (Migliore et al., 1989). These positive data are supported by positive results in numerous in vitro mutagenicity and genotoxicity tests, by in vivo induction of DNA adducts and DNA-protein crosslinks (DPX) at the site of contact and by indications of increases in micronucleus frequency in humans at the site of contact. Based on induction of mutagenic and genotoxic effects of formaldehyde on somatic cells at the site of contact, classification as a Category 2 mutagen is warranted.

Comments received during public consultation

No new information was received during the public consultation.

There was no general agreement on the proposed classification. Four Member States as well as a government agency, two non-governmental organisations and an insurance company expressed their support for the proposed classification. For one Member State questioned the proposed classification. Three industry associations, two formaldehyde producers and an individual disagreed with the proposed classification as a Category 2 mutagen. The justification provided was that classification as a mutagen for different mutagenic categories always refers to germ cell mutagenicity. Since formaldehyde is not bioavailable to the germ cells following relevant exposures, induction of germ cell mutagenicity can be excluded and a classification as germ cell mutagen seems to be scientifically unjustified.

RAC assessment and comparison with criteria

The evaluation of genotoxicity data of formaldehyde by the Dossier submitter and the RAC mainly differed in the assessment of mutagenicity tests on somatic cells of animals and humans at the site of contact. After consideration of all the assessed data, the Dossier submitter and the RAC both came to the same conclusion, namely that classification of formaldehyde as a 'suspected germ cell mutagen' was warranted.

A discussion of the key data and arguments that are relevant to the proposal are found below.

Experimental data

In vitro

Formaldehyde, which induced mutagenic and genotoxic effects in proliferating cells of directly exposed cell lines, should be regarded as an in vitro mutagen with a predominantly clastogenic mode of action. Gene mutation tests gave insufficient evidence for induction of gene mutations.

The substance induced clastogenic effects (such as chromosomal aberrations, increased micronucleus formation and sister chromatid exchanges) as well as genotoxic effects (DPX and DNA adducts) in cultured mammalian cells as well as in cultured human cells.

Results of gene mutation tests (HPRT test in V79: Grafström, 1990; Merck, 1989) were contradictory. The positive result in a mouse lymphoma assay (MLA) (Speit and Merk, 2002) was

based on an increase in the frequency of small colonies, suggestive of chromosomal aberrations. Only a marginal increase in the frequency of large colonies, suggestive of gene mutations, was observed in the study. The positive results of MLA's conducted by Blackburn et al. (1991) and Mackerer et al. (1996) were not evaluated in detail, because no differentiation into small and large colonies was carried out.

In vivo, on somatic cells at site of contact

Formaldehyde was genotoxic in somatic cells at the site of contact. Due to its high reactivity, particularly DPX were induced in the nasal mucosa of rats (≥0.3 ppm) and the nasal turbinates of monkeys (≥0.7 ppm) that were exposed by inhalation. DPX can be induced in proliferating and non-proliferating cells. In proliferating cells, unrepaired DPX can lead to mutagenic effects. Therefore, the ability of formaldehyde to induce such genotoxic effects, which are considered as indicators for mutagenicity, should be taken into account as justification for its classification as a mutagen.

There was not sufficient evidence for induction **of clastogenic effects by formaldehyde** in vivo at a site of contact. In contrast to the Dossier submitter, the RAC concluded that the **existing data for chromosomal mutations** should not be taken into account as justification for the classification of formaldehyde.

Dallas et al. (1992) reported a marginal but statistically significant increase in chromosomal aberrations in the broncho-alveolar lavage cells from rats after inhalation of formaldehyde. This study was not fully reliable due to the high background frequencies of chromosomal aberrations in the negative controls and the lack of a positive control. In a study by Sul et al. (2007), increased DNA damage was observed in lung cells from rats after inhalation of formaldehyde but also without including a positive control. Under experimental conditions comparable to those of Dallas et al. (1992) and Sul et al. (2007), induction of chromosomal aberration in broncho-alveolar lavage cells was not confirmed by Neuss et al. (2010c) in a micronucleus test. It should be noted that the positive control used did not give appropriate sufficient response for micronucleus induction. Consistent with this, no induction of DNA-protein crosslinks or DNA damage was observed in a Comet assay which included a positive control substance, and showed an appropriate response in the lavage cells. Migliore et al. (1989) reported the induction of micronuclei in epithelial cells along the gastro-intestinal tract of rats after oral administration (gavage) of formaldehyde. The result could not be clearly evaluated, because the positive effect was observed only in conjunction with signs of severe local irritation. In addition the positive control was of questionable relevance.

No increase in micronucleus frequency was observed in nasal epithelial cells of rats after inhalation exposure to 20 ppm formaldehyde in a study by BASF (2001a, 2001b) and in a mix of cells from nasal turbinates and nasal septum of rats up to 15 ppm in a study by Speit et al. (2011). As an important limitation it should be noted that only a cell mix without basal cells was used and the positive controls were assessed as not valid. In principle, the results of such tests should be interpreted with caution, because the micronucleus test with nasal epithelial cells is not an established test system and no valid positive control is available to demonstrate the sensitivity of the test system.

In vivo, on somatic cells at distant site of exposure

In vivo studies did no show genotoxic or mutagenic effects.

Current studies showed no induction of DNA adducts (Lu et al., 2010, 2011; Moeller et al. 2011) or DNA-protein cross-links (Speit et al. 2009) in different organs (e.g. spleen, bone marrow). Using standard in vivo genotoxicity tests which are in accordance with international guidelines, Speit et al. (2009) showed that formaldehyde does not induce DPX, SCE or micronuclei in peripheral blood cells of rats exposed by inhalation.

Positive results were not sufficiently reliable because the investigations suffered from methodical limitations (Kitaeva et al., 1990) or the results were biologically implausible in relation to formaldehyde toxicity (Im et al., 2006; Zhao et al., 2009).

In vivo, on germ cells

It has been shown that formaldehyde is not bioavailable to the gonads after inhalation hence it is unlikely to induce germ cell mutations.

Few studies are available regarding the induction of germ cell mutagenicity after intraperitoneal (i.p.) injection. The results of these studies are inconsistent and inconclusive. No information on toxic effects was given. Inadequate test descriptions or methodological limitations (e.g. Odeigah et al., 1997: due to the lack of a positive control, the result of a dominant lethal test is not fully reliable) made it difficult to assess the results. Altogether, no clear conclusion could be drawn that formaldehyde induces mutagenic effects in germ cells after i.p. injection. Therefore the positive results from certain germ cell mutation studies were not taken into account for supporting justification of a formaldehyde classification.

Human data

In humans at site of contact

In studies on localised mutagenicity in humans, formaldehyde exposure was by inhalation and induction of micronuclei was used as the endpoint for genotoxicity. The reported results on induction of micronuclei in buccal and nasal mucosa cells were contradictory.

Although the positive results indicated a possible mutagenic effect in directly exposed human cells, most of the results were not fully reliable due to methodological shortcomings (e.g. large variations in the background frequencies of micronuclei in control populations, variety of staining procedures, no consideration of co-factors). For example, Suruda et al. (1993) reported increased frequencies of micronuclei in buccal cells but not in nasal cells for the same study group. The positive result in buccal cells was very questionable and seemed to be based on the extremely low values in the negative control. There was no information indicating increased mouth breathing. The interpretation of the test results was additionally complicated by the significantly differing data from negative controls in the two cell types. The background frequency of micronucleated cells was considerably lower for buccal cells (out of the normal range) than for nasal cells.
The positive findings for buccal cells and for nasal cells are in contrast to the results of investigations by Speit et al. (2007) and by Zeller et al. (2011) under strictly controlled exposure conditions. These most relevant negative studies were conducted under clearly defined exposure situation and with the same group of subjects before and after exposure. Positive findings in humans are also contradicted by an animal study with well-defined exposures (Speit et al., 2011).

The main reasons for the contradictory results seem to be the lack of standardization of the micronucleus test with exfoliated cells (no consideration that basal cells are able to divide) and the fact that no data were available from a study group which could be used as a positive control. Altogether, it appears not justified to use these conflicting results for the evaluation of the mutagenic potential of formaldehyde.

In humans at distant site of exposure

Contradictory results were obtained for genotoxic effects as well as for mutagenic effects in peripheral blood of humans after inhalation exposure to formaldehyde. Information on co-exposure and other confounding factors is limited in prospective or retrospective studies. From a biological point of view, systemic effects are not expected because formaldehyde exposure does not lead to an increase in formaldehyde concentration in blood. Thus, for induction of primary DNA damage (DPX) as well as for induction of chromosomal aberrations, micronuclei and SCE's in human lymphocytes, no scientific explanations are available.

There are also experimental data from animal studies, which raise questions about the interpretation of positive findings from the human biomonitoring studies.

Altogether, there is not sufficient evidence to conclude that formaldehyde induces systemic genotoxicity in man. Therefore these results were not considered for inclusion in the discussion on classification of formaldehyde.

In humans, on germ cells

No studies investigated the effect of formaldehyde on human germ cells. Due to the extremely low systemic bioavailability, it can be assumed that formaldehyde does not reach the germ cells after inhalation.

Thorough comparison with the criteria and the RAC's conclusions

Classification as germ cell mutagen category 1

Classification of formaldehyde as a germ cell mutagen Category 1A or 1B is not warranted.

ECHA guidance to CLP states in section 3.5.1 that classification of substances for germ cell mutagenicity "is primarily concerned with substances that may cause mutations in germ cells of human that can be transmitted to the progeny". For this purpose, a substance is allocated, based on existing data, to either category 1A, 1B or 2.

The current state of knowledge is that formaldehyde does not reach the germ cells due to its extremely low systemic bioavailability. No evidence of an effect on germ cells by a relevant route of exposure is available.

Classification as germ cell mutagen category 2 ("suspected germ cell mutagen")

Classification of formaldehyde as germ cell mutagen Category 2 "suspected germ cell mutagen" is warranted.

Although the hazard class for mutagenicity strictly refers to germ cells, **the ECHA guidance to CLP considers also the induction of genotoxic effects at sites of contact by substances** which are not bioavailable to the germ cells. Due to its high reactivity, formaldehyde induces genotoxic effects, particularly DPX, at sites of contact in vivo. Regarding the relevance of positive indications from such tests for the classification of a substance, the guidance states, in section 3.5.2.1.2 "With the exception of *in vivo* studies proving 'site of contact' effects, genotoxicity data from such non-standard *in vivo* studies are not sufficient but may offer supporting information for classification". This implies that genotoxicity tests that have been performed on a site of contact are relevant for classification.

Regarding the somatic cell genotoxicity at site of contact the ECHA guidance to CLP clearly says in section 3.5.1 (text bolded by the author of the opinion): "It is also warranted that **where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens**. Classification as a suspected germ cell mutagen may also have implications for potential carcinogenicity classification. This holds true especially for those genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, "site of contact" genotoxicants). This means that if positive results in vitro are supported by at least one positive in vivo, somatic cell test, such an effect should be considered as enough evidence to lead to classification in Category 2."

Formaldehyde induces genotoxic effects in vivo on somatic cells at a site of contact. These positive data are supported by positive results in vitro in numerous genotoxicity and mutagenicity tests. Therefore, a classification as germ cell mutagen Category 2 'suspected germ cell mutagen' is appropriate.

No classification

Based on the induction of genotoxic effects in vivo on somatic cells at site of contact which are supported by positive results in numerous mutagenicity and genotoxicity tests in vitro, formaldehyde should be classified as 'suspected germ cell mutagen', and 'no classification' is not appropriate.

Conclusion on classification

During RAC meetings, the hazard classes on mutagenicity and their interpretation with regard to the classification of somatic cell mutagenicity were discussed on a very fundamental level. It was raised that it should be noted that the classification on formaldehyde was based on the strict

application of the guidance criteria and that there was no scientific indication of germ cell mutagenicity with regard to formaldehyde. The absence of a scientific indication of germ cell effects would be consistent with the weight given in the above justification.
However, due to the induction of genotoxic effects in vivo on somatic cells at site of contact, which are supported by positive findings from mutagenicity and genotoxicity tests in vitro, the RAC agreed that classification of formaldehyde as Muta. 2 in accordance with the CLP Regulation, with the hazard statement H341 (Suspected of causing genetic defects) is therefore warranted. The route(s) of exposure should not be stated in the hazard statement as it is not proven that other routes than inhalation can be excluded. The corresponding classification under DSD is Muta. Cat. 3, R68.

Carcinogenicity

RAC evaluation of carcinogenicity

Animal Data

Summary of the Dossier submitter's proposal

Animal data - Inhalation route

The Dossier submitter concluded that there is sufficient evidence for carcinogenicity of formaldehyde based on squamous cell tumours and other tumours at the site of contact observed in rats of both sexes after ≥ 24 months inhalation exposure to formaldehyde at concentrations above 2 ppm.

In a number of inhalation studies (Woutersen, 1989; Kamata, 1997; Moniticello, 1996; Kerns 1983 and Sellakumar 1985), formaldehyde consistently induced nasal squamous cell carcinomas in rats, as summarised in Table 25.

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

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

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

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

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

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

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

Animal data – Oral route

Increased incidences of squamous cell papillomas in the forestomach of rats receiving formaldehyde with drinking water in the study of Takahashi (1986) was not consistent with two other carcinogenicity studies at similar high doses (Til, 1989 (guideline compliant) and Tobe, 1989). Lymphohaematopoietic tumours have not been reported in any of the three studies. The study of Soffritti et al. (1989) reporting increased incidences of lymphohaematopoietic malignancies and cases of rare gastrointestinal tumours was disregarded, since a re-evaluation in 2002 revealed much higher tumour rates than the original (1989) evaluation.

Animal Data – Dermal route

Three promotion studies with limitations which included the duration of treatment (26-60 weeks) and the number of animals, did not report skin tumours after treatment with formaldehyde alone. It was concluded that convincing evidence of a carcinogenic effect via the dermal route was absent.

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

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

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

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

At higher doses, cytolethality is followed by RCP. An increased rate of cell proliferation is associated with a larger probability of fixing a primary DNA lesion as a mutation and a decrease in the time available for DNA repair. The observed hyperplastic and metaplastic changes strongly support the hypothesis of a mechanism driven by regenerative proliferation accompanied by an inflammatory response that may also result in secondary amplification of the high-dose genotoxic effects of formaldehyde. A steep increase in tumour induction is therefore expected at doses exerting cytotoxicity and RCP, as has been observed experimentally. It is also consistent with the

induction of chromosomal aberrations at the site of contact at high doses (Dallas et al., 1992). Besides, saturation of the glutathione-mediated detoxification of formaldehyde may contribute to the non-linearity of the dose response (McGregor, 2006).

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

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

Comments received during public consultation

Industry stakeholder organisations expressed their concerns regarding the proposed classification as carcinogen Cat. 1A and mutagen Cat. 2, as the proposal was considered not to be science-based or evidence-based, and generally questioned that there was any causal relationship between formaldehyde exposure and formation of nasopharyngeal tumours (NPC) from epidemiological data which was considered inconsistent and (due to a high number of cases in plant 1) biased data. It was highlighted that the upgrading will have tremendous consequences for the industry producing wood-based panels. Medical surveillance activities during the last decades/century did not find a single case of nasopharyngeal cancer. However, no details were reported, and the information is not part of the available published epidemiological data. In their view, setting of limit concentrations is not compatible with the proposed classification. Other parties who provided comments proposed maintaining the current classification until the NCI update is available or to look at similarities with acetaldehyde, which is classified as Carc. 2 (CLP).

Other comments considered that threshold considerations and available information on the mode of action do not justify the proposed classification as a Cat 1 carcinogen under CLP.

A number of comments addressed exposure and risk, while other comments related to other REACH procedures and other regulations-related issues. As a general comment, aspects concerning exposure, risk estimation or risk management, however, are not relevant for harmonized classification according to the CLP Regulation, in contrast to the intrinsic properties of the substance of concern.

The majority of comments received during public consultation addressed the evidence from human information, but a number of comments also referred to animal data. Some comments followed the specific provisions as given in the CLP guidance to suggest their view on the justification for classification on carcinogenicity. A single commenter did not regard experimental data from rats as the best model to extrapolate to humans and primate data were considered more relevant.

With regard to carcinogenicity distant from the site of contact, it was emphasized that relevant tissues were not sufficiently investigated in all carcinogenicity studies. This observation was confirmed by the Dossier submitter for the studies of Monticello (1996), Feron (1998), Woutersen (1989) and RAC notes that the presence of distant tumours may also be masked by high rates of nasal tumours and tumour-related mortalities.

RAC assessment and comparison with criteria

Carcinogenicity at the site of contact

Animal data - Inhalation route

Available carcinogenicity studies in animals with publication dates ranging from 1982 to 1996 were conducted, as usually seen in studies from this era in whole-body exposure chambers. None of these exposed animals were via head-only or nose-only tubes.

In **rats,** formaldehyde caused nasal tumours in both sexes at concentrations above 2 ppm. The incidences of squamous cell carcinoma, the dominant tumour type, increased with a steep slope from 5.6 ppm onwards and reached maximum rates of 38-47% at formaldehyde concentrations around 15 ppm. In addition, increased rates of adenocarcinomas, rhabdomyosarcomas and undifferentiated carcinomas or sarcomas were observed from 10 ppm.

At 2 ppm, no malignant tumour response was observed in nasal tissues, but the study of Kerns (1983) revealed increased rates of benign nasal tumours (papillomas, polyploid adenomas) from 2 ppm onwards. The absence of a dose-response relationship at higher concentrations is not critical as malignant nasal tumours may 'overwrite' benign tumours in the histopathology evaluation. Signs of inflammation and regenerative proliferation (nasal epithelial hyperplasia) in the nasal cavity were also observed in studies from 2 ppm. Dysplasia of nasal epithelia that may indicate transformation to early precursor tumour cells were also seen from 2 ppm onwards.

Malignancies in the nasal tissues were observed in rats at concentrations of 5.6 ppm and above. Taking putative precursor lesions and benign tumours into account the LOAEC for neoplastic and corresponding preneoplastic/benign tumour responses is 2 ppm. Based on the available data, no such findings were observed at concentrations up to 1 ppm in rat studies (NOAEC for nasal tumours in rats).

In **mice,** the overall database is small, as only one inhalation carcinogenicity study is available. This study (Kerns, 1983) reported a small, non-significant increase in nasal squamous cell carcinomas (2%) at the highest dose in males only (14.3 ppm). Two out of 108 male mice exposed to the high concentration of 14.3 ppm developed nasal squamous cell carcinomas. The relative percentage of 2% is however an underestimate, since only a small fraction of animals was kept until the end of the 24 months of treatment. In this study, the total of 119-120 males and 120-121 females/group were divided into sub-groups for interim sacrifice: 10 mice/sex/group were sacrificed after 6 and 12 months, 0-1 male and 19-20 females at 18 months, 17-21 males and 26-41 females at 24 months and 0 male and 9-16 females at 27 months. The two nasal tumours were observed in the group of 17 high dose males that were killed at the end of 24 months of treatment. In relation to those animals, the incidence of squamous cell carcinomas in mice should be corrected to 11.7%.

The same tumour was not observed in lower dose groups or in control animals. Inflammation of the nasal mucosa, squamous metaplasia and epithelial dysplasia was observed from 5.6 ppm onwards. Kerns (1983) reported that by 24 months, more than 90% of mice in the 14.3 ppm group had dysplastic and metaplastic alterations and rhinitis. At 27 months (at the end of 3 additional months of recovery), dysplastic and metaplastic lesions were still evident in more than 40% and 20% of females (no survivors in males), respectively (for additional information from Kerns et al., 1983, see reference No. 22: Preliminary report in: Gibson et al., 1983). Information on carcinogenicity at concentrations higher than 14.3 ppm to establish a dose-response relationship is not available.

In conclusion, formaldehyde caused comparable cytotoxic, metaplastic and dysplastic nasal effects including nasal tumours in mice and in rats. However the only available study in mice has limitations due to low animal numbers (compared to present standard of 50 animals/sex/group) that received formaldehyde until the age of 24 months. Mouse data suggest a lower sensitivity to formaldehyde-induced cytotoxicity and nasal tumour induction in this species compared to rats. EPA (2010) explained this difference at least in part by a higher decrease in minute volume (- 75% in mice vs. – 45% in rats, a response that is also known from other compounds with irritating properties on the respiratory tract) and thereby a lower inhaled dose in mice (approximately two-fold lower at same formaldehyde concentration). These findings are in agreement with one comment received during public consultation (see RCOM) reporting that formaldehyde is a nasal irritant, leading to reflex depression of the respiratory rate and minute volume in rats and mice. This response is much more pronounced in mice as compared to rats (Chang et al., 1981, 1983; Jaeger and Gearhart, 1982) leading to a markedly reduced delivered dose at the nasal surface in mice in comparison to rats. The difference in delivered dose is a good semi-quantitative explanation for the different responses of rats and mice to nasal tumour induction (Barrow et al., 1980, 1986).

In **hamsters,** no nasal tumours were reported in a life-time study (Dalbey, 1982) with 10 ppm (5 hour/day, 5 days/week) and 30 ppm (5 h once weekly). Hyperplastic and metaplastic areas were seen in the nasal epithelium of 5% of hamsters at 10 ppm. The results from the dose group that received 30 ppm were less reliable due to their single exposure per week design. This study has other major flaws compared to guideline requirements, the major one being that histopathology diagnostic for nasal tumours was only conducted if macroscopically dense areas above 1 mm were observed in sections.

Based on the limited hamster data, the nature of findings observed at 10 ppm was similar to those seen in rats. In both species hyperplastic and metaplastic findings in the nasal epithelium were reported. Absence of tumour response at 10 ppm in hamsters may indicate lower sensitivity than in rats. However due to study limitations, no conclusion on carcinogenicity in hamsters can be taken from this study. No valid study is available for this species.

In conclusion, on inhalation carcinogenicity in animals, formaldehyde via inhalation is considered to be carcinogenic in the rat, and some evidence of carcinogenicity was seen in the mouse (taking into account the overall small database for this species and the low numbers of animals/group that were sufficiently long exposed). No valid data are available for hamsters.

Based on the available data, it is not justified to conclude that there is a significant (in a qualitative way) difference between animal species.

Animal data – Oral route

Three oral studies with a 2-year treatment period and one 32-week study are available with rats. No oral long-term studies on other species were available.

The only treatment-related finding, squamous cell papillomas in the forestomach in 8/10 rats exposed to 0.2% (2000 mg/l) for 32 weeks (Takahashi et al., 1986), was not confirmed in other studies. The most valid carcinogenicity study of Til (1989) applied a comparable concentration of 1900 mg formaldehyde/l drinking water and observed focal ulceration of the forestomach, papillary hyperplasia of the limiting ridge (frequently located at the borderline between forestomach/stomach), chronic atrophic gastritis, ulceration and glandular hyperplasia of the stomach, but no papillomas at doses up to 82 mg/kg/d in males and 109 mg/kg/d in females. Erosive-ulcerative lesions and hyperplasia in the limiting ridge area and absence of papillomas was consistently found in the studies of Tobe et al. (1989) and Takahashy et al. (1986).

In conclusion, oral exposure to concentrations of 0.19% formaldehyde in drinking water consistently caused erosive-ulcerative lesions and (regenerative) hyperplasia in the limiting ridge area in three studies. The RAC agreed with the Dossier submitter that the induction of benign tumours in the forestomach in Takahashi (1986) is considered equivocal.

Animal data – Dermal route

No valid carcinogenicity study using the dermal route is available.

No increase in skin tumours was observed in three promotion studies where mice received formaldehyde only for treatment periods of 26 to 60 weeks with once or three times per week dosing. Dose groups of initiation/promotion studies using genotoxic initiators are not considered relevant for classification on formaldehyde.

In conclusion, no valid information is available to conclude on formaldehyde's potential to cause skin tumours and no conclusion on its carcinogenic potential via the dermal route can be drawn.

Mode of action considerations: **Key events in carcinogenicity at the site of contact**

The present understanding of the mode of action is that the carcinogenicity of formaldehyde in animals is related to a cascade of cellular events following the initial cytotoxic effect of formaldehyde at the site of contact, the upper respiratory tract. With respect to the effects of formaldehyde at the site of contact, the RAC noted the conclusion of the Dossier submitter that experimental results and mechanistic data support a threshold type dose-response relationship for induction of nasal tumours with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role at doses above this threshold. This issue is considered of relevance for its decision on the classification category of carcinogens.

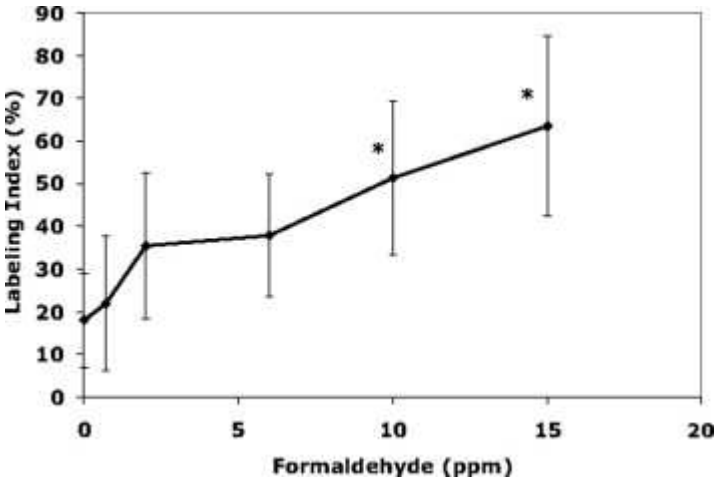
The Dossier submitter concluded that: "Experimental results and mechanistic data therefore support the existence of a threshold type dose-response for induction of nasal tumours with regenerative cell proliferation being the predominant feature in the carcinogenic process".

The RAC agreed with this conclusion of the Dossier submitter that consistent evidence from many

studies indicates that regenerative cell proliferation secondary to cytotoxicity highly correlates with incidences and regional distribution of nasal tumours. Thus increased cell replication at the primary site of contact is considered to be one key event that precedes tumour development.

The study of Monticello et al. (1996) (among others) was identified as the key study on formaldehyde-related cell proliferation response, until in 2010 Meng et al. provided new data using a similar study design (with same dose groups) in a 13-week study with immunohistochemical BrdU-labelling instead of radiographic detection of ^{3}H-thymidine labelled cells in S-phase. The Meng et al. (2010) study focussed on the anterior lateral meatus of the rat nose, which is the site of the highest formaldehyde flux and which has been identified as the site of highest proliferative activity in the Monticello study.

Cell proliferation significantly increased in the anterior lateral meatus of the noses of rats exposed to formaldehyde at 10 or 15 ppm. The percentages of BrdU-labelled cells (proliferating cells) were 18%, 22%, 35%, 38%, 51% and 64% for the 0, 0.7, 2, 6, 10, or 15 ppm, respectively, formaldehyde-treatment groups.



(Figure redrawn from fig.6 in Meng et al., 2010)

* Dunnett's test P<0.01

The Dossier submitter considered increased cell proliferation at 6 ppm as borderline. Significantly higher cell proliferation rates were found at ≥ 10 ppm based on data from eight animals/dose. The almost linear curve on cell proliferation activities demonstrated a concentration-related increase from the lowest concentration onwards with a plateau at 2 and 6 ppm; a level of significance of $p<0.05$ was used. The RAC considered that a level of response where cell proliferation has doubled compared to the level in non-treated animals, could be interpreted as a LOAEC for a biological meaningful response taking into account the limited number of animals. In this case the LOAEC for increased cell replication was already reached at 2 ppm (35%, roughly two-fold the 18% seen in controls). No increase in cell proliferation was observed at 2 ppm in the Monticello study (the value was even lower than the control level).

As a result of increased cell proliferation, both the presence of papillomas (the benign type of squamous cell tumours) and polypoid adenomas at 2 ppm (Kerns, 1983) and the evidence of epithelial hyperplasia observed at the same concentration (2 ppm) (Kamata, 1997) supported the conclusion that 2 ppm is the LOAEC for increased cell proliferative activity. Epithelial dysplasia (35/40 rats), squamous metaplasia (24/40 rats) and adenomatous polyp (1/40) (the latter two effects require cell proliferative activity for their development) after 18 months of formaldehyde exposure to 2 ppm supported a LOAEC of 2 ppm (Swenberg et al. 1980). The LOAEC of 2 ppm was also supported by other recent studies (Andersen et al., 2008 (Table 3 of Annex 1 to this opinion), Andersen et al., 2010 (Table 2 of Annex 1)) who found nasal lesions consisting of inflammation, squamous cell metaplasia, and epithelial hyperplasia at 2 ppm and higher. The LOAEC might actually be lower, as similar effects were occasionally seen at 0.7 ppm in these studies.

However, some (non-significant) increase in cell proliferative activity was also found at 0.7 ppm (22% vs. 18% in controls) and the fact that no clear threshold dose could be estimated up to 15 ppm would also allow the interpretation that the cell proliferative response increased linearly with

the concentration of formaldehyde.

A recent study did find small, but significantly increased cell proliferation at 0.5, 1 and 2 ppm (Speit et al. 2011). However, the most sensitive sub-sites of the nasal turbinates (lateral meatus, nasoturbinate, nasopharynx) showed non-identical proliferation rates at different concentrations and monotonic dose-responses for each single region (e.g. considering only lateral meatus at level 1) was observed above 2 ppm.

The Dossier submitter found that the steep increase in tumour induction is also consistent with the conclusion drawn by McGregor (2006), who stated that mechanistic events of significance for carcinogenicity occur at dose levels where formaldehyde detoxification mechanisms are saturated. McGregor referred to the original data of Casanova and Heck (1987), who demonstrated greater DPX concentrations in GSH-depleted rats (by phorone pretreatment) than in normal rats that were exposed for 3 h to 0.9, 2, 4, 6 or 10 ppm formaldehyde. In this study DPX concentrations at formaldehyde concentrations up to 10 ppm were clearly below those in GSH-depleted rats at the same formaldehyde dose. In fact, Casanova and Heck actually did not show whether formaldehyde alone reduces GSH concentrations. Cassee and Feron (1994) observed that rats exposed to 3.5 ppm formaldehyde for 8 hours had increased glutathione peroxidase (GPX) concentrations, but did not find reduced nasal tissue GSH levels at this dose level. Casanova et al (1989) estimated that the glutathione dependent pathway is half-saturated at 2.6 ppm. As DPX formation is induced in nasal tissues at low concentrations of ≥0.3 ppm in rats and ≥0.7 ppm in monkeys (no lower concentrations examined), saturation of GSH detoxification mechanisms appears not to be critical for the formation of DPX in the low concentration range.

Lowest concentration of nasal tumour response in rats

Two of the available carcinogenicity studies (Table 25 of the BD, see also above) indicated 6 ppm formaldehyde to be the lowest concentration at which squamous cell carcimomas were seen in rats. The presence of papillomas (the benign type of squamous cell tumours) and polypoid adenomas at 2 ppm (Kerns, 1983) supported by the presence of dysplastic epithelium (a tumour precursor lesion) at 2 ppm (Kamata, 1997) indicate that 2 ppm is the LOAEC for the early tumour response. Spontaneously, nasal tumours in rats are very rare (roughly estimated as below 0.1% for squamous cell carcinomas according to several sources) and as cell replication rates and tumour incidences show concentration-related response, 2 ppm should be considered as the lowest concentration associated with increased proliferation rates and early tumour responses in rats.

Genotoxicity at the site of contact plays a role above the threshold of cell proliferation

In agreement with the Dossier submitter's view, DPX formation in proliferating cells is considered relevant for genotoxic effects and subsequent tumour development. DPX formation in nasal mucosa was demonstrated after a short exposure to formaldehyde (see 4.9.1.2.1 of the BD). DPX can be eliminated by spontaneous hydrolysis and/or other DNA repair mechanisms. Incomplete DNA repair in proliferating cells is known to lead to mutations (for review see Barker et al. 2005) and tumour development.

A critical question is whether DPX formation may occur at lower concentrations than cytotoxicity and whether this may then indicate that DPX formation may occur independently of cytotoxicity.

Indications of regenerative cell proliferation (expressed as mucosal/epithelial hyperplasia or transformation to squamous metaplasia) following cytotoxicity were found in the long-term studies at formaldehyde concentrations of 2 ppm and higher (see above). Thus the presence of DPX at low concentrations (< 2 ppm) is of interest.

Marked increases in DPX yields were observed in susceptible nasal regions of the rat at 6 ppm and above. Dose-related increases in DPX were already seen at concentrations of 0.3, 0.7 and 2 ppm (Casanova et al., 1989). The amount of DPX/mg DNA at 0.3 ppm was considered to be comparable to those that can be found in urban or indoor environments that may (or may not) pertain to endogenously generated formaldehyde. Heck and Casanova (1994) (as cited in Casanova et al., 1994, see Table 1 therein) confirmed a tendency for increased DPX at 2 ppm (3 hour exposures) (no data on lower concentrations).

Although a number of studies examined DPX formation at low concentrations, it appears that the overall database is not sufficient to estimate the dose-response curve below 2 ppm. Detailed data

on numerical increases are missing for some studies and the increase can only be roughly estimated from figures. The non-linearity is mainly attributable to the dose range between 2 ppm and 6 ppm. Thus the dose response below 2 ppm could be linear or may have a threshold (below 0.3 ppm) that has not been identified (at least by the animal studies available).

RAC considerations on threshold modes of action for key events

Taking the LOAEC for increased cell proliferation/precursor lesions of 2 ppm and the presence of increased cell proliferation and increased DPX below 2 ppm into account, it cannot be concluded with certainty that cytotoxity is the initial lesion that triggers all secondary effects including DPX formation. DPX formation below 2 ppm leads to the assumption that DPX formation and cytotoxicity may occur in parallel. Two options may be discriminated (1) DPX at 'normal' cell proliferation rates' and 2) DPX at significantly increased cell proliferation':

1) At formaldehyde concentrations at which a 'normal' cell proliferation rate is seen (below 2 ppm), DPX may be formed, which in turn can induce primary mutagenic effects and may theoretically lead to tumour development. DPX formation can be repaired by hydrolysis or enzymatic repair mechanisms and thus the likelihood of tumour development is assumed to be low. Studies showed that DPX levels are increased in a concentration-related manner in this dose range. However, similar levels of DPX during a 3-hour exposure after prolonged pre-treatment for 11 weeks compared to single 3-hour exposure (without weeks of pre-exposure) provide evidence that DPX formation at low concentrations of 0.7 and 2 ppm will not accumulate during prolonged exposure to formaldehyde (Casanova et al., 1994). Uncertainty remains about the non-significant increases in DPX observed at 0.7 ppm and 2 ppm compared to controls, because these were not included in this study.

In vitro studies in different cell lines demonstrated that DPX formation was accompanied by mutagenic effects such as TK mutations (small colonies), DNA single strand breaks and micronuclei formation (Speit and Merck, 2002; Cosma et al. 1988 a,b; Speit et al. 2000). In vivo, manifestation of mutagenicity, which is associated to DPX formation at concentrations below 2 ppm were found in the study of Dallas et al. (1992) as chromosomal aberrations in BAL (bronchoalveolar lavage) cells from rats exposed to 15 ppm. However the study was considered to be not fully reliable due to the lack of positive controls and the unusually high levels for negative controls. Another study from Migliore et al. (1989) reported induction of micronuclei (a clastogenic effect) in gastrointestinal cells after oral administration of 200 mg/kg. Also, this study had flaws, as the chosen positive control substance gave negative results and the positive effects were observed only in conjunction with severe local irritation. In conclusion, there is insufficient data to show the presence or absence of mutagenic effects in cells (in response to persistent DPX formation) at the site of contact, in particular for the low dose range (below 2 ppm).

A number of studies reported increased numbers of micronuclei in buccal and nasal cells of humans (see 4.9.2.1 in the BD). The Dossier submitter concluded that these studies reveal indications of local genotoxic effects in humans. However, a standardised study protocol for this type of study is not available. The majority of studies did not continuously monitor exposure conditions (e.g. at the work place), did not consider confounding factors such as co-exposure to other substances and micronucleus frequencies of the negative/background controls varied significantly. The only study in humans conducted under strictly controlled exposure conditions, (Speit et al., 2007) did not find micronuclei in buccal cells of volunteers after inhalation exposure to concentrations up to 0.5 ppm at the end of treatment for 4 h/d during 10 working days and at 7, 14, and 21 days thereafter. The results of this study can be interpreted that for the low dose range (up to 0.5 ppm formaldehyde), there were no indications of micronuclei after 10 days of inhalation exposure for 4 hours daily. A more recent study on nasal cells of non-smoking volunteers during light activities exposed to formaldehyde under similar strictly controlled inhalation exposure (4 h/d, 5 days) to concentrations of 0.3 and 0.7 ppm (with peaks of 0.8 ppm) revealed no increase in micronuclei in nasal mucosa cells compared to pre-exposure values (Zeller et al. 2011). It is important to note that these high quality studies which did not find micronuclei at low doses (below 2 ppm), were contradictory to a number of studies that did find micronuclei in buccal and/or nasal cells. Thus, uncertainties remain in the interpretation of the database to judge low dose effects, in particular that small increases in DPX do not contribute to an increased risk for nasal cancer.

2) At formaldehyde concentrations with higher cell proliferation (at/above 2 ppm), DPX may

induce mutagenic effects that with higher likelihood (due to the dose-related increased cell proliferation rate) will be manifested as tumours. This assumption is consistent with the significantly increased nasal tumour rates seen in rats from 6 ppm onwards and the first benign nasal tumours seen at 2 ppm.

Observations relevant to identifying the threshold for identified key events for the mode of action:

Cell proliferation	DPX formation
• Statistically significant increases in cell proliferation at ≥ 6 ppm • Doubling of cell proliferation (considered to be biologically meaningful) at 2 ppm • Linear dose-response for increased cell proliferation at 0.7 ppm and higher • No clear threshold identified • Limited data on dose-response below 2 ppm • Manifestation of increased cell proliferative activity as mucosal hyperplasia and squamous metaplasia at 2 ppm and higher	• Statistically significant, non-linear increases in DPX formation at ≥ 6 ppm • Indications of dose-related DPX formation at 0.3 ppm and higher • No clear threshold identified • Limited data on dose-response below 2 ppm (insufficient information on non-linearity or linearity) • No accumulation of DPX after prolonged exposure up to 2 ppm • Manifestation of mutagenic effects (e.g. micronuclei production) following DPX formation is assumed to be low below 2 ppm (inconsistent data from numerous positive studies against some well-controlled human studies up to 0.5 ppm) • Saturation of formaldehyde detoxification is not relevant below 2 ppm

Conclusions on a threshold mode of action

Overall there are indications of a threshold at 2 ppm (LOAEC) for cell proliferation (as indicated from hyperplastic/metaplastic/dysplastic precursor lesions and increased cell proliferative activity) and DPX formation, and this LOAEC can be considered to point to 'practical threshold' for the effects.

However data also indicate non-significant dose-related increases in cell proliferative activity and DPX formation below 2 ppm. Taking into account the overall limited database below 2 ppm, no firm conclusion on the presence of a biologically meaningful threshold, the existence of linearity of dose-response curve in the low dose range (< 2 ppm) for both effects can be made.

Tumour response is non-linear and shows steep increases at concentrations above 6 ppm

The Dossier submitter concluded that a steep increase in tumour incidences was observed in rat carcinogenicity studies at concentrations above 6 ppm. However, non-linearity at concentrations above 6 ppm does not provide information on the curve in the low dose range and therefore there is no information on whether or not there exists a threshold below which no tumour response can occur.

The Dossier submitter referred to the possibility that saturation of formaldehyde dehydrogenase (essential for the formate pathway) could be considered to explain the non-linearity of the tumour response at concentrations above 6 ppm. The steep increase in tumour rates has been interpreted to indicate that glutathione-dependent detoxification may have become saturated. The glutathione and glutathione-dependent formaldehyde dehydrogenase (synonym for alcohol dehydrogenase 5) dependent pathway is half-saturated in the nasal epithelium of the rat at 2.6

ppm formaldehyde (Casanova et al. 1989). The concentration-response relationships for DPX formation, cytotoxic effects, proliferative response and tumours are highly non-linear, with a significant increase of the slope at concentrations of around 4 ppm, a concentration at which glutathione-mediated metabolism is known to be saturated (Casanova and Heck 1987). In contrast, the slope of the curve for cell proliferation activity in rats in the Meng study (2010) does not allow a break point concentration to be identified, which may indicate that saturation of the glutathione-mediated detoxification was not reached at concentrations up to 15 ppm.

Relevance of animal data for humans

The RAC agreed with the argumentation of the Dossier submitter that the differences in formaldehyde deposition in the upper respiratory tract between rats and humans, the differences in anatomy and in breathing patterns (exclusive nasal breathing versus oronasal breathing) lead to differences in the local dosimetry. Although the carcinogenicity of formaldehyde has not been tested in primates, which are considered to be more similar to humans, Monticello (1989) has demonstrated that inhalation of 6 ppm formaldehyde for 1 or 6 weeks induced loss of cilia, inflammatory response, epithelial hyperplasia and squamous metaplasia and increased cell proliferation in the nasal passages of rhesus monkeys. Like in rats, lesions in monkeys showed an anterior-posterior gradient and duration-related increase in severity and extension of lesions, but these were more widespread than in rats. Increases in cell proliferation were observed in the nasal passages, larynx, trachea and lung carina of monkeys that correspond to DPX formation in these regions (Casanova, 1991). The observed toxicity and carcinogenicity of formaldehyde in the respiratory tract of rats is therefore considered highly relevant for primates and humans. Differences in localisation (e.g., increased cell proliferation was also demonstrated in the nasopharynx of rhesus monkey, Monticello et al., 1989) correspond to the nasopharynx as the main tumour site in humans and may explain the prevalence of nasal tumours in rats (and mice) and the nasopharyngeal area as the major target site in humans.

Similarities in the type of tissues affected in the respiratory tract and presence of key enzymes across species and occurrence of key events – cytotoxicity, increased cell proliferation, epithelial hyperplasia and squamous metaplasia seen in rats, mice and monkeys support the conclusion that the identified mode of action is similar across species and is relevant to humans, for whom no microscopic data on the nasal and nasopharyngeal epithelium after repeated/chronic exposure are available.

Systemic Carcinogenicity

Increased rates of lymphohaematopoietic malignancies were identified in workers exposed to formaldehyde. Therefore the analysis of animal data in this document focusses on the evidence for formaldehyde's carcinogenic potential on lymphohaematopoietic tissues.

Animal data – Inhalation route

The Dossier submitter noted that there was no evidence of induction of tumours at distant sites and that, particularly in the lymphohaematopoietic system, conclusions were based on findings obtained from inhalation carcinogenicity studies in **rats.** However most studies were not adequately designed to detect tumours in organs other than the respiratory tract (see Table 17 of the BD). A full histopathological analysis of all tissues was not performed in these studies (Monticello 1996; Feron 1998; Woutersen 1989). No increase of lymphohaematopoietic tumours was found in the studies of Kerns et al. (1983) which included histopathological examination of 50 organs/tissues in rats. A non-significant increase in lymphomas was seen in female mice at 15 ppm (22% vs. 19% in controls). The long-term inhalation study in hamsters did not examine organs other than the respiratory tract (Dalbey, 1982).

The lymphoid tissues of the upper respiratory tract are not routinely the focus of a detailed histopathologic examination in carcinogenicity studies of the 1980's and 1990's since enhanced histopathology techniques are necessary to obtain reliable data. In order to find indications of proliferative activity in the submucosal lymphoid tissues and lymph nodes of the upper respiratory tract, and to obtain information on possible associations between formaldehyde inhalation exposure and lymphohaematopoietic tumours in animals, additional investigations were conducted. The nose-associated lymphoid tissue (NALT) of rats and mice of the Kerns study (1983) has been re-evaluated, and this revealed squamous metaplasia of the epithelium covering the NALT and inflammation in the NALT at 15 ppm, increased incidences of germinal centre

development in rats at 2 and 6 ppm (at 6 and 12 months interim sacrifices) and at 15 ppm (12 months) (Kuper, 2007, 2012) and no effects in mice. A formaldehyde exposure-related effect was neither detected on incidences of leukaemia in rats nor on the incidences of lymphomas in male mice (Woutersen, 2007). A positive trend was concluded for lymphomas in female mice (at 6 and 15 ppm), however incidences at 15 ppm (45%) were not significantly different from control incidences (50%). The effects, however, do not show a clear dose-response relationship when all doses are taken into account (2, 6, and 15 ppm) and any relationship to treatment appears questionable, due to the high control incidence and absence of lymphomas in male mice. In 2011, subacute inhalation studies (Kuper, 2011) reported hyperplasia of the lymphoepithelium and increased cell proliferation of the epithelium in the follicular and interfollicular area of the nasal lymphoid tissue (NALT) in rats at 15 ppm and no effect in mice at concentrations up to 15 ppm (Kuper 2011). The observed epithelial hyperplasia in the area of the nasal lymphoid tissue is difficult to interpret with respect to the lymphohaematopoeitic system being a target in humans. While the retrospective analysis of the Kerns study showed some (limited due to the lack of dose-response) evidence indicating an increased lymph cell activity in the absence of elevated rates of leukaemia in rats after chronic exposure, no such effect has been observed after a subacute inhalation study.

In conclusion, no indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumours resulted from an inhalation carcinogenicity study on rats and mice (Kerns et al (1983)).

Animal data – Oral route

No increase in lymphohaematopoietic tumours has been reported from three studies (see Table 16 of the BD). Among these, a comprehensive list of organs/tissues was exclusively examined in the study of Til (1989). Tobe (1989) performed histopathological examination on selected organs only (bone marrow and thymus were not included), which were limited to the stomach and other organs (not specified) in the peritoneal cavity, in the study of Takahashi (1986).

An increased incidence in lymphohaematopoietic tumours was reported by Soffritti et al. (1989, 2002). However their study was considered as non-valid, since their re-evaluation in 2002 resulted in markedly higher incidences of lymphohaematopoietic tumours (about two-fold in all dose groups).

In conclusion, no evidence on lymphohaematopoietic tumours was provided by the study of Til (1989), and evidence from Soffritti (1989) studies was considered equivocal. At present no firm conclusion can be drawn for carcinogenicity by the oral route.

Animal data – Dermal route

No valid carcinogenicity study using the dermal route is available and the three available initiation/promotion studies in mice do not provide evidence of tumours at sites other than the skin.

In conclusion, no valid information is available to conclude on formaldehyde's potential to cause tumours at distant sites and no conclusion on the systemic carcinogenic potential for the dermal route can be drawn.

Conclusion on systemic carcinogenicity - all routes

Finally, none of the carcinogenicity studies in rats (1 oral, 1 inhalation), which were considered valid, provided evidence of lymphohaematopoietic tumours. The inhalation study in mice (Kerns et al., 1983) did not find increased rates of lymphomas in formaldehyde exposed animals.

No conclusion can be drawn for systemic carcinogenicity for the oral route in the mouse.

No conclusion can be drawn for systemic carcinogenicity for the dermal route for the mouse.

No data on systemic carcinogenicity are available for the hamster (all routes) and for the rat for the dermal route

Overall the RAC agreed with the view of the Dossier submitter that the available data did not provide evidence of a carcinogenic effect at distant sites.

RAC evaluation of carcinogenicity (continued)

Human data

Summary of the Dossier submitter's proposal

According to the DS, classification as Carc. 1A is warranted for formaldehyde, due to its potential for induction of nasopharyngeal cancers (NPC) in humans.

The proposed classification Carc. 1A is based on the finding of increased mortality due to nasopharyngeal cancer in humans, and is supported by the increased frequency of tumours in the nasal cavity of rats exposed by inhalation to formaldehyde. No other cancers, including leukaemia and myeloid leukaemia were causally associated with exposure to formaldehyde in humans or rats. Evaluation of carcinogenic potency in humans has been found difficult, because the lack of precise exposure measurements do not allow a reliable dose-response curve to be established.

Cohort studies were performed on two types of exposed workers:

- industrial cohorts of workers from formaldehyde production plants, resin plants or other industries using formaldehyde or
- professional cohorts of embalmers or anatomo-pathologists.

Industrial cohorts

Three large, recently-updated, industrial cohorts are considered to be the most informative: the NCI cohort (Beane Freeman, 2009 and Hauptmann, 2004), the British cohort (Coggon, 2003) and the NIOSH cohort (Pinkerton, 2004). The metrics of exposure of workers were estimated based on monitoring data and assessments made by project industrial hygienists.

Table 1. Exposure characteristics of the three main industrial cohorts

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

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

In the NCI cohort (Hauptmann 2004), which is the most important industrial cohort available in terms of size and duration of follow-up, a 2-fold increase in the risk of nasopharyngeal cancer (statistically significant, standardised mortality ratio (SMR) 2.1 (95% CI 1.05-4.21)) was found. The increase is supported by positive trends in relative risks with peak exposure (p trend <0.001) and with cumulative exposure (p trend = 0.03). This excess (based on a regression analysis using the low-exposure category as reference) was confirmed when comparing the NPC mortality with local rates to take into account regional environmental factors (Marsh 2005). In this post-hoc analysis it was noted that most NPC cases occurred in one plant (plant 1), of 10 plants studied. Further investigation of this NCI cohort (Marsh et al., 2007b) demonstrated that risk estimates for NPC in the NCI cohort are unstable, mainly because of the rarity of NPC and the difficulty of

providing evidence of association with exposure for small increases in rare cancers. This means that small changes in the observations might lead to rejection of the hypothesis; which is due to the fact that there are very few cases, and these few cases are clustered in plant 1.

In this study (Marsh et al., 2007b), a non-significant increase in the relative risk for NPC in the highest exposure category was however observed even after adjustment for plant group. Marsh et al. (2007a) also further investigated plant 1 of the NCI cohort in a nested case-control study, with the hypothesis that the excess of NPC in plant 1 can be due to external employment in the ferrous and non-ferrous metal industries that entailed possible exposure to several suspected risk factor for upper respiratory system cancer (e.g., sulphuric acid mists, mineral acid, metal dust and fumes). A statistical association between NPC and working in silver-smithing or other metal work has been identified. However, a non-statistically significant association between NPC and formaldehyde was still observed. The odds ratio (OR) for formaldehyde exposed after adjustment for smoking and working in silver-smithing or other metal work was 2.87 (95% CI 0.21-infinity) after adjustment for this factor. Positive trends were found as well with duration of employment and with cumulative exposure, but not with average intensity.

No increase in the risk of nasopharyngeal cancer (NPC) or other cancers was observed in two other industrial cohorts: the British cohort (Coggon, 2003) and the NIOSH cohort (Pinkerton, 2004).

Professional cohorts

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

No significant increase in the risk of nasopharyngeal cancer or most other cancers was observed in any of the studied professional cohorts: British pathologists (Hall, 1991), US embalmers (Walrath, 1983, US embalmers (Walrath, 1984)), Canadian embalmers (Levine, 1984), American anatomists (Stroup, 1986) and American embalmers (Hayes, 1990), except for the following findings:

- US embalmer cohort (Walrath, 1984): a weak increased of proportional mortality ratio due to prostate (PMR =1.8, 95% CI 1.1-2.6) and colon cancer (PMR =1.9, 95% CI 1.3-2.7).
- American anatomists (Stroup, 1986): increased mortality due to brain cancer (SMR=2.7, 95% CI 1.3-5.0), myeloid leukaemia (SMR=8.8, 95% CI 1.8-25.5)
- US embalmer cohort (Hayes 1990): all cancers: white men (SMR=1.1); lymphohaematopoietic cancers: white men (SMR=1.3, 95% CI 1.1-1.6), non-white men (SMR=2.4, 95% CI 1.4-4.0); myeloid leukaemia, white men (SMR=1.6, 95% CI 1.0-2.4); unspecified leukaemia: white men (SMR 2.1, 95% CI 1.2-3.3), non-white men (SMR=4.9, 95% CI 1.0-14.4).

Case-control studies

Fifty three case-control studies of cases - diagnosed or died due to various cancers - were reported in the CLH report. The frequency of occurrence of formaldehyde exposure in occupational history assessed in various ways in cases with cancer was compared with the frequency of such exposure in appropriate control cases not diagnosed with cancer.

Cancer of the nasal cavity and sinuses: 9 case-control studies:

- four studies showing statistically significant OR above 1 showing that formaldehyde exposure, particularly high exposure in occupational histories of cancer cases, could occur more frequently than in control cases without cancer (see Table 4.10.2.3 in the CLH report);

- in five studies the OR were not significantly elevated[2]

Oral cavity cancer: 2 case-control studies

- in two studies non-significantly elevated OR for formaldehyde exposure

Salivary gland cancer: 1 study

- 2405 subjects who died from salivary gland cancer between 1984-1989 in 24 states of the US had significantly elevated OR=1.6 (95% CI 1.30-2.00) but only for mid-high probability/mid-high intensity of exposure to formaldehyde

Nasopharyngeal cancer: 8 case-control studies

- 2 studies showing statistically significantly elevated OR for formaldehyde exposure
- 6 studies showing non-significantly elevated OR or not demonstrating elevated OR for formaldehyde exposure

Pharyngeal cancer: 5 case-control studies

- in one study, OR for formaldehyde exposure significantly elevated
- in five studies, OR for formaldehyde exposure non-significantly elevated or not elevated

Laryngeal cancer: 7 case-control studies , 6 non-significantly elevated OR or negative, 1 positive (significantly elevated OR)

Lung cancer: 6 case-control studies: 5 non-significantly elevated OR or negative, one positive (significantly elevated OR)

Lymphohaematopoietic malignancies: 8 control studies, 5 non-significantly elevated OR, 3 significantly elevated OR

Brain cancer: 1 case-control study: non-significantly elevated OR

Bladder cancer: 1 case-control study: not increased OR

Rectal cancer : 1 case-control study: significantly elevated OR

Uveal melanoma: 1 case-control study: significantly elevated OR

Oesophageal cancer : 1 case-control study: non-significantly elevated OR

Pancreatic cancer: 1 case-control study: positive , low increase OR 1.1-1.4

Thyroid cancer : 1 case-control study: significantly elevated OR

(see information in 4.10.2.3, Table 21 of the BD)

Meta-analysis:

In the meta-analysis by Partanen et al. (1993), NPC risk was elevated with statistical significance in the substantial exposure category (exposure exceeding 5.5 ppm/year). NPC risk was also significantly elevated in Blair et al. (1990) and in Collins et al. (1997). Two recent meta-analysis (Bosetti 2008 and Bachand 2010) have highlighted the role of the NCI cohort and in particular the impact of plant 1 in the overall increase in risk. An overall increase in risk of borderline significance in pooled case-control studies was however observed in Collins et al. (1997) and in Bachand et al. (2010) (see Table 22, 4.10.2.4 in the BD).

Dossier Submitter's conclusion

Overall, in the opinion of the Dossier submitter, there is consistent evidence from the NCI cohort and from several case-control studies that formaldehyde may induce NPC. The existence of a grouping of cases in plant 1 of the NCI cohort raises doubt that the excess is caused by occupational exposure to formaldehyde and lowers the level of evidence but it can also be

[2] For the figures representing the OR values see the background document in Annex 1.

explained by the largest number of subjects exposed to high peaks in this specific plant. The DS did not consider that that there is sufficient evidence of a causal relationship between formaldehyde exposure and other cancers, including myeloid leukaemia.

Comments received during public consultation

Comments from several Member States (Denmark, Germany, Malta, Poland, Sweden and The Netherlands), companies/industrial associations and non-governmental organisations/trade unions were received, see Annex 2 to the opinion. Relevant text passages of a range of comments are also compiled in the Appendix to the opinion document.

RAC assessment and comparison with criteria

Industrial cohorts are the preferred means of establishing a causal association with a chemical in an industrial setting, mainly because the populations studied can usually have their exposure well characterised, whether expressed as a cumulative exposure or average intensity of exposure. However, for rare diseases, it is difficult to determine important excesses, especially as non-significant results are likely to go unreported or unrepresented in such cases. There is also an additional concern that the statistical significance over any excesses of rare diseases might be exaggerated due to small sample bias. Cohort studies often report on mortality data, rather than incidence data, the latter being usually preferred for cancers where prognosis is relatively good.

Case-control studies are preferred to occupational cohort studies when studying rare diseases, because it is usually possible to study incidence cases and the studies can be powered to detect relatively modest excesses in risk. However, such studies are often population-based, and occupational exposures are not always of primary interest. Exposures are usually assessed retrospectively and are often based, even when assessed by industrial hygienists, purely on job title. Unlike what is usually done in cohort studies, case-control studies usually allow risk estimates to be adjusted for other important known and suspected risk factors for the diseases. Hence case-control studies and industrial cohort studies have different strengths and weaknesses when looking for evidence for carcinogenicity from rare cancers.

For the RAC, the main issue to be considered on tumours at the site of contact that may be linked to inhalation exposure to formaldehyde is on NPC. As this is a rare tumour, a number of studies looked at the pharynx as a tumour site which included the nasopharynx as a part of it. It appears reasonable to assume that at a late stage of tumour development, when causing mortalities, uncertainties may arise about the primary site of tumour origin. Given this, RAC considered case-control studies on the pharyngeal area (including nasopharynx and hypo- and oropharynx) and adjacent tissues (sino-nasal tissue, larynx, oral cavity) that may also have relevance for this opinion. The pharynx was covered by the buccal cavity in the Hauptmann study (ICD 140-149) and nasopharynx cancer-related mortalities were separately analysed (ICD 147). The nasopharynx was merged with other pharynx tumours (ICD 146-149) in the summary tables of the studies of Coggon (2003) and Pinkerton (2004).

Epidemiological cohort studies

Solid cancers at the site of contact: Nasopharyngeal/pharyngeal/laryngeal tumours

In the British industrial cohort study (Coggon, 2003), comprising 14 014 industrial workers with a follow-up up to 70 years (Gardner et al., 1993; Coggon, 2003), no excess of risk of mortality due to nasopharyngeal cancers was observed. Increases in mortality from lung cancer (SMR = 1.58, 95% CI 1.40 to 1.78) were noted; however, the excess of deaths from lung tumours was reduced when the comparison was made with local rates, rather than national ones and did not increase with duration of employment in high-exposure jobs or with time since first employment in a high-exposure job. A small increase in the number of deaths from pharyngeal tumours (including the nasopharynx) (SMR 1941-2000, 1.55 (0.87-2.56), SMR 1990-2000, 2.02 (0.87-3.99)) was observed in the total cohort and in the high exposure group (> 2 ppm) (SMR, 1.91 (0.70-4.17). Only one death from nasopharyngeal carcinoma (2.0 deaths expected) occurred and the man concerned had not worked in a job with high exposure to formaldehyde. No measurements of formaldehyde had been taken before 1970, but from later measurements and from workers' recall of irritant symptoms, it is estimated that the background exposure corresponded to time-weighted average concentrations of less than 0.1 ppm (0.12 mg/m^3); low exposure to 0.1–0.5 ppm (0.12 mg/m^3- 0.6 mg/m^3); moderate exposure to 0.6–2.0 ppm (0.72 mg/m^3- 2.4

mg/m^3); and high exposure to greater than 2.0 ppm (2.4 mg/m^3) (ca. 4000 workers). Some of the exposures may have occurred through inhalation of paraformaldehyde particles or particles of formaldehyde-based products. Mortality was also increased for stomach cancer (SMR = 1.53, 95% CI 1.17 to 1.95). Mortality from leukaemia and other lymphatic and haematopoietic cancer was lower than expected from national rates, both in the full cohort and in the subset of men with high levels of exposure. In addition to formaldehyde, other hazardous materials, including styrene, ethylene oxide, epichlorhydrin, various solvents, asbestos, chromium salts, and cadmium, were handled at some of the factories. In most cases, however, any exposures to these substances would have been relatively low. Smoking data was not collected as part of this study. The authors concluded that a small increase in the risk of sino-nasal and/or nasopharyngeal cancer cannot be ruled out from the results of their study.

When a job was once assigned to the exposure category according to the job title and from allocation through measurements (reported not to be available before 1970) and from worker's recall of irritant symptoms, the job remained in the same exposure category for all time periods. Considering that the highest exposures to formaldehyde were expected to occur during the earlier years of production and that the duration of working-time in a certain job area was not considered, allocations to exposure categories may show uncertainties. If a man worked in several jobs, he remained classified to the highest exposure category he worked in. Thus exposures in the high exposure group may be overestimated, which would reduce the detection of exposure-related tumours assuming that tumour response is related to a high concentration of formaldehyde.

The study's statement that no measurements of formaldehyde had been taken before 1970 suggests that measurements were available after 1970. However quantitative estimates of formaldehyde exposures cannot be found in the Coggon study (2003) or its precursor studies. Exposures were classified as high, moderate, low or background on the basis of subjective information from persons including management with long experience of the working conditions (Acheson et al., 1984). Turnover of employees was reported to be 36% in the first year and 61% within five years.

The workers' memory of symptoms indicating irritancy is not an objective measure of exposure. It is not clear how subjective information was translated into high, moderate and low. It remains unclear whether 'high' graded symptoms attributed to a concentration above 2 ppm were validated by measured data.

Subjects were placed into one of the exposure subcategories, SMRs were only determined for lung and stomach cancers of each exposure group. For tumours at other sites (including pharyngeal tumours), SMRs were determined for the whole cohort and the high exposure group.

The ability of the study to detect increases in rare tumours such as the nasal/nasopharyngeal tumours is very limited due to the poor statistical power (17% for the >2 ppm group or 44% for the total cohort, BfR, 2006; EPA, 2010). Thus a study showing low risk and wide confidence intervals is considered to be consistent with increased risk seen in the NCI study as the former does not necessarily give evidence that there is no association between formaldehyde exposure and cancer. Moreover, there is the possibility that the result is a false negative.

Cancer-related mortalities were only accounted for in the upper respiratory tract, if the tumour was regarded as the cause of death. Deaths from other reasons may have masked tumours in this area. This was obvious for sino-nasal cancers. While no deaths related to sino-nasal cancer were recorded in the update period from 1999-2000 (0.8 deaths expected), two cases of sino-nasal cancer were registered in men whose deaths were ascribed to other causes and who worked in jobs with high exposure. Hence, in such cases, it might be better if a cancer incidence study rather than mortality study was carried out.

Conclusion: The study of Coggon et al. (2003) did find a small, but non-significant increased risk of nasal/pharyngeal tumours. This result has to be interpreted in the light of insufficient ability to detect increases in tumours due to poor statistical power. With respect to nasal/pharyngeal tumours the study does not allow any conclusions to be drawn.

The NIOSH cohort study (Pinkerton 2004) included 11 039 workers (82% females) with start of exposure in 1955-1959 and with minimum exposure periods of three months. The mean time weighted average for formaldehyde exposure at three plants in the early 1980s was 0.15 ppm

(0.18 mg/m^3, range 0.09 -0.20 ppm), lower than in NCI and British cohorts, although past exposures may have been substantially higher. Area monitoring showed that formaldehyde levels were essentially constant without peaks or intermittent exposures (survey data from a total of 549 measurements in different working areas from 1981 and 1984, published in the precursor study, Stayner et al., 1988). It is stated that no other chemical exposure was identified which could result in confounding of the study results. The vital status of all persons in the cohort was determined until 31 December 1998, which provides a maximum of 40 years of follow up. While the vital status of the workers was updated in the Pinkerton (2004) study, the work histories were not, as it was assumed that exposure ceased in 1981 for plants 1 and 2 and in 1983 for plant 3. Standardised mortality ratios (SMR) were calculated on three categories (duration of exposure (<3, 3-9, ≥10 years), time since first exposure (<10, 10-19, ≥20 years) and year of first exposure (<1963, 1963-70, >1971). Mortality from all causes (2206 deaths, 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 0.80-2.37) 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. For the total cohort, mortality from pharyngeal cancer (3 deaths observed, SMR 0.64, CI 0.13-2.59), laryngeal cancer (3 deaths observed, SMR 0.88, CI 0.98-1.86) and trachea, bronchus and lung cancer (147 deaths, SMR 0.98, CI 0.82-1.15) was not increased. 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. Multiple cause mortality from leukaemia was increased almost two-fold 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). Multiple cause mortality from myeloid leukaemia among this group of workers was also significantly increased (8 deaths, SMR 2.55, 95% CI 1.10 to 5.03). The study authors concluded that the study had limited statistical power, since the power to detect a two-fold or greater increase in mortality from nasopharyngeal cancer or from nasal cancer was only 13% and 16%, respectively.

Measurements were conducted in 1981 and 1984 and were used to confirm the low variability of exposure levels in the plants. Persons were not allocated to different exposure levels. The exposure level of this study is low (TWA 0.15 ppm) and probably too low to assess a concern for high formaldehyde exposure. The calculation of SMRs on pharyngeal tumours was limited to the total cohort; SMRs were not calculated for the metrics duration, time since first exposure and year of first exposure (which makes sense due to the low observed tumours). There was no control or background group. In this study multiple causes of death were registered and analysed.

Conclusion: The Pinkerton study did not assess dose-related tumour responses. The analysis for nasal/pharyngeal tumours is limited to comparing observed cases from exposed persons with expected cases from national rates at a poor statistical power and at a low exposure level. With respect to nasal/pharyngeal tumours the study does not allow RAC to draw any conclusion.

The NCI cohort (Beane Freeman, 2009 and Hauptmann, 2004) consists of the largest number of followed up industrial workers (ca. 25 600) exposed to formaldehyde and working in 10 different plants. In addition to SMRs compared with the US population, this cohort was investigated using local external and internal reference populations for risk calculations.

Subjects were followed from the year of initial plant identification (i.e., the year in which employment records were thought to be complete; range, 1934–1958) or first employment at a plant, whichever was later:

- until January 1, 1980 (Blair et al., 1986),
- then until December 31, 1994 (Hauptman, 2004) and
- until December 2004 (Beane Freeman et al., 2009, – only the lymphohaematopoietic malignancies study was published, the study on solid tumours is still on-going and has not been published).

There are also a number of other studies aimed at elucidating uncertainties in the interpretation of the data from this cohort.

Exposure to formaldehyde was estimated by the study authors (Blair, 1986; Hauptman, 2004; Beane Freeman et al., 2009) from work histories based on job titles, tasks, visits to the plants by study industrial hygienists, discussions with workers and plant managers, and monitoring data. Peak exposures were defined as short-term excursions (generally less than 15 minutes) that exceeded the 8-hour, time weighted average formaldehyde exposure. Peak exposures in the workplace occurred from routine (e.g. hourly, daily, or weekly) or non-routine performance of high-exposure tasks or from working in areas where non-routine, unusual upsets or events, such as spills, occurred.

Since no measurements of peak exposure were available in this study, peaks and their frequency (hourly, daily, weekly, or monthly) were estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average. For the extended follow-up, no information on formaldehyde exposure after 1980 was obtained.

The following formaldehyde exposure metrics were calculated as time-dependent variables: cumulative exposure (ppm-years), average exposure intensity (ppm), duration of exposure (years), highest peak exposure category (non-exposed, >0–<0.5 ppm, 0.5–<2.0 ppm, 2.0–<4.0 ppm, ≥4.0 ppm), exposure to formaldehyde-containing particulates (ever/never), duration of exposure to each of 11 other substances (years), and duration of working as a chemist or laboratory technician (years).

The authors (Hauptmann et al., 2004) assessed the presence of particulates to represent formaldehyde as a solid (e.g., paraformaldehyde ortrioxane), formaldehyde-containing resins, molding compound particulates, or particulates onto which formaldehyde gas could be adsorbed. Exposures to 11 known or suspected carcinogens and other widely used chemicals in the plants were evaluated (antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene).

Standardized mortality ratios (SMR) within the entire cohort were used to compare mortality with external US general population and relative risks (RR) were estimated to compare mortality within various subpopulations defined according to exposure metrics within studied cohort.

Results of the first study (Blair et al., 1986) demonstrated that in the cohort followed until 1 January, 1988, the workers exposed to formaldehyde had slight excesses for Hodgkin disease and cancers of the lung and prostate gland, but these excesses were not consistently related to duration of or average, cumulative, or peak formaldehyde exposure levels.

Results of the second follow-up until 31 December, 1994 (Hauptmann et al., 2004) revealed that compared with the US population, mortality from all solid cancers was significantly lower than expected among subjects exposed and non-exposed to formaldehyde (SMR = 0.91 (95% CI 0.87.0.96) and 0.78, (95% CI 0.70-0.86) respectively). Nasopharyngeal cancer was the only cause of death leading to non-significant increases in SMR among members of the cohort exposed to formaldehyde (SMR 2.10, exact 95% CI 0.91 - 4.14, observed deaths 8) but also among the cohort members non-exposed to formaldehyde (SMR 1.56, 95% CI 0.39 – 6.23, observed deaths 2). The incidence of tumours was also non-significantly higher in exposed workers than in the US population for the nose and nasal cavity (SMR 1.19, 95% CI 0.38-3.68, observed deaths 3) and for the bone (SMR 1.57, 95% CI 0.75-3.29, observed deaths 7). The statistical power to detect a two-fold increase in tumour-related mortality for NPC based on the comparison of all exposed workers with general population was poor (calculated to be 9%, BfR, 2006). The increased SMR of 2.1 for risk of nasopharyngeal cancer as such (not regarding the positive trends, see below) is regarded as borderline, because there is some evidence that relative risks from epidemiological studies, based on small numbers of cases, may have exaggerated levels of statistical significance (Greenland 2000).

The authors noted in the discussion of these results, that 47% of the subjects were ever occupationally exposed to at least one of the following substances: antioxidants (22%), asbestos (14%), carbon black (11%), dyes and pigments (16%), hexamethylenetetramine (15%), melamine (28%), phenol (14%), plasticizers (20%), urea (27%), wood dust (10%), and benzene (2%). Relative risks for various cancers and formaldehyde exposure categories did not change substantially when adjusted for duration of exposure to these substances, except for nasopharyngeal cancer and melamine exposure. For that site, relative risks for the highest exposure categories of peak and average intensity of formaldehyde exposure declined when the analysis was adjusted for melamine exposure (data not shown), but trend tests remained

significant for peak, average and cumulative exposure. Exposure to melamine occurred at six plants, mainly in the manufacture of synthetic resins with formaldehydes. Unfortunately the authors did not provide values of SMRs for subpopulations of the investigated cohort stratified according to exposures to other substances, particularly wood dust, asbestos, carbon black or others so their potential confounding effect does not seem to be fully eliminated. It is further noted that five of the nine deaths from nasopharyngeal cancer occurred at one plant. For the chosen metrics of this plant, the adjusted relative risks for the peak exposure was 1.00 (not applicable due to absence of deaths) for the low and mid peak group and 9.07 for the high peak group ≥4 ppm (p-trend 0.008), 1.00 (p-trend not applicable), 8.51 and 23.54 for average intensity (p-trend 0.404), 2.18, 1,00, 1.34 and 5.32 for cumulative exposure (p-trend 0.0007); and 1.76, 1.00, 1.21, and 8.59 for duration of exposure (p-trend 0.043). These results were found to be consistent with increasing SMR with increasing cumulative exposure and duration of exposure to formaldehyde in an independent investigation of workers at this plant (Marsh et al., 2002).

The further analysis in this paper (Hauptmann et al. 2004) was focused on the internal comparisons within investigated cohort of the relative risk of death due to solid cancers in subpopulations of the cohort stratified according to formaldehyde exposure metrics. The workers assigned to low-exposure category were used as the reference in internal analyses for calculation of relative risks to minimize the impact of any unmeasured confounding variables, since non-exposed workers may differ from exposed workers with respect to socioeconomic characteristics. For calculation of risk of nasopharyngeal cancer, the unexposed population was used as a reference population for internal comparison, when there was lack of cases in the low-exposure category. If positive, the calculation of RR among the low exposure group and groups with higher exposure metrics gives stronger evidence on test substance induced tumour-related mortalities than a comparison of ever exposed workers with general population.

According to internal comparisons the relative risks for nasopharyngeal cancer (nine deaths) increased with average exposure intensity, cumulative exposure, highest peak exposure, and duration of exposure to formaldehyde (p-trend = 0.066, 0.025, <0.001, and 0.147, respectively); trends were significant for the cumulative exposure and peak exposure. The relative risk for the highest peak exposure ≥ 4 ppm was 1.83. Hauptmann created several alternative maximum peak exposure metrics, ignoring peaks in jobs of short duration (< 6 or < 12 months) or rare peaks (less often than daily or weekly) from the calculations and found relative risks of 2-7 in this group. However, 4 cases out of 7 nasopharyngeal cancer deaths in the exposed group occurred in the subpopulation of workers that had peak exposure > 4 ppm and were exposed to formaldehyde less than 5 years, which raise the question whether short-term exposure to formaldehyde may be sufficient for tumour development.

Formaldehyde exposure did not appear to be associated with lung (SMR 0.97, 95% CI 0.90-1.04), pancreas (SMR 0.83, 95% CI 0.67-1.04), or brain (SMR 0.92, 95% CI 0.68-1.23) cancer. According to the authors (Hauptmann et al., 2004) in this cohort of formaldehyde-industry workers, some evidence was found of an exposure-response relationship with mortality from nasopharyngeal cancer (based on 7 cases in the exposed group and 2 in non-exposed group), but not for cancers of the pancreas, brain, lung, or prostate.

To examine the hypothesis of a causal association between formaldehyde exposure and mortality from nasopharyngeal cancer the original data for the cohort provided by authors (Hauptmann et al., 2004) were re-examined using the alternative methods of data analysis and alternative categorizations of formaldehyde exposure (Marsh and Youk, 2005). Re-evaluation by Marsh and Youk (2005) revealed that six of 10 nasopharyngeal cancer deaths observed in the NCI study occurred in only one plant (Plant 1, Wallingford plant) and the remaining four cases occurred individually in four of the other nine plants studied (plant 2, 3, 7 and 10). No NPC deaths were observed in plants 4-6, 8 and 9.

A large, statistically significant, regional rate-based SMR due to nasopharyngeal cancer death equal to 7.39 (95% CI 2.71 – 16.08) and US-based SMR 6.62 (95% CI 2.43 – 14.40) was only found among formaldehyde-exposed workers in plant 1. In plants 2-10 (ca. 21 000 workers) regional rate-based SMR due to nasopharyngeal cancer death equal to 0.98 (95% CI 0.27- 2.51) or US-based SMR amounting to 0.96 (95% CI 0.26- 2.45) demonstrate that formaldehyde exposure did not increase a risk of nasopharyngeal cancer death among members of a large cohort of 21 335 workers ever employed in plants 2-10 of the original NCI cohort.

It was further found that statistically significant exposure–response relationship with formaldehyde and nasopharyngeal cancer reported by Hauptmann et al. (2004) for highest peak exposure was driven entirely by the large, statistically significant excess NPC risk observed for plant 1 in the highest peak exposure category (≥4 ppm). For the remaining nine study plants (Plants 2–10), which comprised 21 358 workers or 80% of the NCI cohort, there was no evidence of an exposure–response relationship using NCI's highest peak exposure metric. In fact, the RRs for all non-baseline exposure categories of highest peak exposure were less than 1.0.

Table 2. Selected characteristics and findings of the Marsh and Youk study (2005)

Plant No.	Entry year	No. subjects	% subjects ever in the highest peak category	No. subjects ever in the highest peak category	Observed deaths for NPC	SMR-US	SMR-local
1	1943	4261	46.1	1964	6	6.62*	7.39*
2	1945	784	91.6	718	1	5.35	6.74
3	1949	2375	0	0	1	1.99	4.18
4	1958	1692	72.9	1233	0	0.00	0.00
5	1957	744	20.4	152	0	0.00	0.00
6	1951	5248	2.0	105	0	0.00	0.00
7	1938	4228	0.4	17	1	1.06	1.31
8	1934	1679	1.1	18	0	0.00	0.00
9	1956	1933	9.3	180	0	0.00	0.00
10	1941	2675	69.7	1864	1	1.44	1.10
Total				6252			

* Statistically significant

The table above shows that the percentage of workers exposed at the highest peak category was largest in plant 2, 4 and 10, where no statistically significant increase in NPC risk was observed, while plant 1, where there was an excess of NPC deaths, was only in the fourth place. The number of workers in the highest peak category in plant 10 (1864 workers) was comparable with the number of workers in plant 1 in that exposure category (1964 workers). This finding may be used to reject the hypothesis that excess of NPC deaths in plant 1 was mainly due to the largest number of subjects exposed to high peaks in this specific plant.

The results of the epidemiological investigation of the industrial cohort of workers employed in plants 2-10 of the NCI cohort support the hypothesis that industrial exposure to formaldehyde does not lead to an increased risk of death due to nasopharyngeal cancer and it contrasts with findings in plant 1 of that cohort.

Considering all three industrial cohorts of ca. 50 000 workers exposed to formaldehyde (Coggon, 2003, Pinkerton, 2004; Hauptmann et al. 2004; Marsh and Youk, 2005) it may be concluded that the hypothesis of a causal association between formaldehyde exposure and mortality from nasopharyngeal cancer is supported only by evidence coming from the investigation of 4261 workers employed in plant 1 (Wallingford plant), one of the 10 plants investigated within NCI cohort (Hauptmann et al. 2004; Marsh and Youk, 2005). It is however possible that this unique grouping of NPC cases in this one plant influencing the outcome of the entire NCI cohort could be the effect of factors other than exposure to formaldehyde, since three workers of the Wallingford plant (Table 3) had acquired NPC tumours after a very short period of employment on a job with formaldehyde exposure as revealed by Marsh (2012)[3].

[3] "*Formaldehyde and Nasopharyngeal Cancer: What Have We Learned from the Epidemiology Studies?"* presentation by Marsh G.M. at the Formaldehyde International Science Conference, Madrid, Spain (April 2012)

Table 3. Characteristics of duration of exposure of 7 persons with nasopharyngeal cancer in a subgroup of NCI cohort (Wallington cohort) exposed to formaldehyde's exposure peak ≥ 4 ppm

No. of the person	Duration of exposure (years)	Average exposure (ppm)
1	0.62	0.13
2	**0.25**	0.03
3	17.87	0.60
4	4.28	0.16
5	**0.15**	0.14
6	**0.01**	0.07
7	35.20	0.19

(Marsh, 2012) Bold figures indicate exposures shorter than 6 months

Taking into account that duration of formaldehyde exposure for 3 cases was from few days to 3 months their causal relationship between formaldehyde exposure and nasopharyngeal cancer does not seem very probable – however regarding the local genotoxicitiy of formaldehyde and evidence of similar effects in animals it could not be excluded. A study in animals showed persistence of squamous metaplasia in 65% and basal cell/pseudoepithelial hyperplasia in 15% of animals after 3 months inhalation of 9.2 ppm formaldehyde and recovery until 25 months (Woutersen et al., 1989). One squamous cell carcinoma and one polypoid adenoma was observed in a group of 30 rats.

To elucidate the apparent discrepancy in NPC risk estimates between most of the industrial cohorts (Coggon, 2003; Pinkerton, 2004; Hauptmann et al., 2004; Marsh and Youk, 2005) the cohort of workers working in plant 1 (Wallingford plant) was investigated thoroughly to identify factors associated with the NPC excess.

Marsh et al. (2002) investigated the extended cohort of 7328 workers ever working in this Wallingford plant 1 in the years 1941-1984, with their vital status followed until 1998. This 1998 follow-up included all Wallingford workers at risk during 1945-1998 (n=7328 or 99.6% of the total population). More than 1300 workers (18%) were employed for ten or more years, and more than 60% of the total cohort has now been followed for 30 or more years. The exposure estimation was based on an examination of the available sampling data and job descriptions as well as on verbal descriptions of jobs and tasks by plant personnel, including the plant industrial hygienist. The exposure assessment revealed that the median average intensity of exposure (AIE) to formaldehyde for the 5665 exposed workers (0.138 ppm) was lower than the current Occupational Safety and Health Administration (OSHA) standard of 0.75 ppm (OSHA, 1992). The median formaldehyde AIE was slightly higher for the 5104 workers exposed to formaldehyde in jobs with non-product particulate exposure (0.20 ppm) and among the 2523 workers exposed to formaldehyde in jobs with pigment exposure (0.20 ppm). The median AIE of long-term workers was at least twice as high as that for short-term workers.

Apart from this retrospective cohort study, the nested case-control study of nasopharyngeal cancer and other pharyngeal cancer (PC) was performed by Marsh at al. (2002). During the 1945-1998 study period, 22 PC deaths were identified among the Wallingford cohort and were included as cases in the nested case-control study. These deaths included the following findings at specific sites: oropharynx (n=5), nasopharynx (n=7) and hypopharynx (n=3), as well as deaths coded to the residual category: 'pharynx, unspecified' ($n_{=}7$). Each cancer case was matched on race, sex, age and year of birth (within two years) to four controls from the remaining living and deceased members of the cohort. Information on lifetime smoking history and relevant exposures outside of Wallingford was collected through structured telephone interviews with the respondent or a knowledgeable informant (usually a surviving family member). Fifteen (68%) of the 22 PC cases were interviewed, including five (71%) of the seven NPC cases and ten (67%) of the 15 'other PC' cases. Interviews were obtained for 76% of 88 targeted controls.

Cohort result (Marsh at al., 2002): Based on local county (US) rates, a statistically significant

2.23-fold (95% CI 1.4-3.38) (US SMR 2.63 fold, 95% CI 1.65-3.98) excess for PC combined and a statistically significant five-fold (95% CI 2.01-10.30) (US SMR 4.94, 95% CI 1.99-10.19) excess based on seven deaths for NPC, the primary site of *a priori* interest, was found for plant 1 (7328 workers). During the 1985-1998 update period an additional three deaths from NPC and six deaths from 'other PC' were found. The 1985-1998 SMR for NPC was 4.89 (based on 0.61 expected deaths) and this was statistically significant. However, it was noted that short-term workers with employment less than 1 year and long-term workers with exposure above 1 year experienced similarly elevated SMRs for both PC and NPC categories. Most PC (18 cases) and NPC (6 out of all 7) cases occurred among workers hired between 1947 and 1956, resulting in the largest and statistically significant SMRs of 3.24 and 8.13, respectively. There was little consistent evidence of increasing mortality risks with increasing levels of the formaldehyde exposure measures considered. For NPC, limited evidence of an association was observed with increasing duration of exposure to formaldehyde, cumulative exposure to formaldehyde or duration of employment in jobs with formaldehyde exposures > 0.2 ppm or > 0.7 ppm. Statistical power to detect a two-fold increase in NPC or pharyngeal tumour-related mortalities was not calculated, but was assumed to be below that of the studies of Pinkerton and Coggon and too small for subgroups on exposure metrics.

In the nested case-control study (Marsh at al., 2002) the exact conditional logistic regression modelling for all PC combined revealed that among the potential confounding variables considered in the univariate models, only smoking history and year of hire (1947-1956) were statistically significant predictors of pharyngeal cancer occurrence. The estimated OR of pharyngeal cancer among workers who ever smoked was 8.03, which is higher than the risks observed for pharyngeal cancer in other case-control studies. However, most of the models adjusted for smoking and year of hire yielded similar OR estimates as the corresponding models unadjusted for these factors suggesting generally weak confounding effects of smoking and year of hire. This nested case-control study was also limited by the inability to acquire information on potential confounding factors, such as exposure to relevant occupational or non-occupational risk factors outside the Wallingford plant.

These potential confounding factors outside the Wallingford plant were investigated in a subsequent study of Marsh et al. (Marsh, 2007a). This reference contained a cohort study on plant 1 and a nested case-control study. In the plant 1 cohort, significantly higher SMR for pharyngeal tumours, for nasopharyngeal tumours only and for all pharyngeal tumours (except nasopharynx) were found. Statistical significance was retained even after adjustment for local mortality ratios. This nested case-control study was aimed at investigating further the possibility that the large nasopharyngeal cancer mortality excess among a cohort of formaldehyde-exposed workers may be related to occupational factors external to the study plant. In this study (Marsh 2007a) occurrence of formaldehyde occupational exposure in 23 nasopharyngeal cancer cases including 7 NPC (plant 1 of NCI cohort) were compared with 92 controls matched for age, sex, race and year of birth from the same cohort. Five of seven NPC cases worked in silver smithing (including brass plating and other jobs related to silver or brass) or other metal work (including steel working and welding), while this type of work was relatively rare in the remaining study population without NPC. The OR was not significantly elevated for frequency of formaldehyde exposure in occupational history, but was significantly elevated for silver smithing (OR=14.41, 95% CI 1.30-757.8, 4 cases), and for silver smithing and other metal work (combined) (OR=7.31, 95% CI 1.08-82.1, 5 cases), suggesting that earlier or later employment of members of the Wallingford plant cohort in silver smithing or other metal work could be responsible for excess of NPC in that cohort. Marsh also found a statistically significant interaction between the risk for plant 1 compared to plants 2-10, which could not be simply explained by differences in exposures between plant 1 and the other plants in the NCI study.

It would be useful to know how frequently workers of the other 9 plants of NCI cohort had also episodes of working in silver smithing or other metal work because such knowledge could substantiate a hypothesis whether or not this type of work is a confounding factor in studying NPC etiology. OR were non-significantly increased for formaldehyde (OR 1.51 (95% CI 0.20-∞) and increased further with duration and cumulative of exposure.

In this study, the observed significantly increased and high OR for the silver smithing may be considered as indicating that the increased risk for NPC was linked to silver smithing and to silver smithing or other metal work. The small increase of OR for formaldehyde exposure may lead to the conclusion that NPC is more strongly associated with silver smithing than to formaldehyde

exposures. However, the estimates were calculated on an ever or never basis, on a small number of 23 cases (including the 7 cases from plant 1), and thus confidence intervals were very large. Consequently the estimated risk ratios are subject to considerable uncertainties. The RAC's view is that a conclusion from the limited data from this study can neither be drawn for silver smithing and other metal work nor for formaldehyde exposure.

Marsh at al. (2007a) provided a literature review in order to support such hypothesis: *"Many exposures and job types associated with the three groups in the operations in the ferrous and non-ferrous metals industry have been linked with increased risks of upper respiratory cancer, although the evidence is not unequivocal. For example, in 1992 IARC classified occupational exposures to strong inorganic-acid mists containing sulphuric acid as carcinogenic to humans (Group 1) based on sufficient epidemiological evidence. In particular, mineral acid and sulphuric acid mists and vapours have been associated with increased risks of upper respiratory tract cancers, including nasopharynx (NPC) (Ho et al., 1999; Li et al., 2006), larynx (Soskolne et al., 1984, 1992; Forastiere et al., 1987; IARC, 1992; Coggon et al., 1996; Steenland, 1997; Steenland et al., 1998; Sathiakumar et al., 1997). Soskolne et al. (1984) found a positive association between sulphuric acid and all upper respiratory cancer sites combined that was strongest for laryngeal cancer."* In the silver and other non-ferrous metal operations such as nickel, brass, imitation gold and copper, the general pickling solution is a 10–25% hot sulphuric acid solution with 5–10% potassium dichromate.

Exposures to metal dusts, wood dusts and industrial heat exposure have been linked to increased risks for NPC, only wood dusts and industrial heat exposure remained significantly higher after adjustment for confounders (Armstrong et al., 2000). In this study each case was matched to only one control (including several controls per case, which improves statistical power). Recently, Shangina et al. (2006) found that laryngeal cancer has been linked to hard alloys dust (OR 2.23 (95% CI 1.08-4.57)) and chlorinated solvents. Hypopharyngeal cancer risk was significantly associated with exposure to mild steel dust and iron compounds and fumes. However, no clear dose-responses for duration and cumulative exposure were seen and uncertainties were raised by the small number of cases (between 1 and 11 per group/metric).

With respect to the latter two studies (which Marsh made reference to in his literature analysis), no conclusion on the association of metal dust with exposure related tumours can be drawn.

Further on in the same review, Marsh concluded that *"epidemiology studies that have evaluated cancer risks in relation to occupation or job type also have found increased risks for: laryngeal cancer among metal manufacturing workers (Goldberg et al., 1997); NPC among primary metal workers and machinists (Huebner et al, 1992), and hammersmiths, welders, flame cutters, metal grinders, polishers, tool sharpeners and machine tool operators (Zheng et al., 1992); and sino-nasal among workers in basic metal industries (Olsen, 1988) and metal and foundry workers (Combra et al., 1992)."*

According to Marsh the analysis of the above data suggest that the large nasopharyngeal cancer mortality excess in the Wallingford cohort may not be due to formaldehyde exposure, but rather reflects the influence of exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulphuric acid mists, mineral acid, metal dusts and heat) during external employment in the ferrous and non-ferrous metal industries.

As the RAC could not examine the literature of risk factors for pharyngeal tumours EPA's assessment (EPA, 2010) is given here:

> *'There are no prior citations of an association between silversmithing exposures and nasopharyngeal cancer in the medical literature, but Marsh et al. review the literature pertaining to related exposures (sulphuric acid mists, metal dusts) and respiratory and laryngeal cancer to support this association. However, the results for these exposures and laryngeal cancer are inconsistent, and data pertaining to these exposures and nasopharyngeal cancer are quite limited. Despite these limitations, Marsh et al. (2007) suggest that the observed associations between nasopharyngeal cancer and formaldehyde exposure in the Wallingford plant are due to these other occupational exposures. Marsh et al. (2007) do note that history of silversmithing and other metal work was not associated with formaldehyde exposure, and so was not a confounder of the formaldehyde results as reported for the Wallingford Plant.'*

Conclusion:

The RAC came to the conclusion that the assumption that the NPC in plant 1 are linked to the exposure to other substances such as silver smithing, metal dust or other substances is not substantiated. Silver smithing does not appear to be an established risk factor for NPC. The estimated higher risk for NPC through silver smithing was uncertain. The findings of significantly increased SMR for pharyngeal and nasopharyngeal tumours in the cohort study support the results of the NCI study.

It is important to note that epidemiological investigations of the industrial cohorts (British cohort, NIOSH cohort and the NCI cohort, if only plants 2-10 were regarded) did not reveal significant association between formaldehyde exposure and risk of death due to nasopharyngeal cancer (Coggon 2003, Pinkerton 2004, Marsh and Youk, 2005).

Case-control studies

Nasopharyngeal/pharyngeal/sino-nasal tumours

Evidence from case-control studies should be taken into account for the overall evidence for an association between formaldehyde exposure and tumours at the site of contact.

The study groups in case-control studies are defined by the presence of tumours, and data on formaldehyde exposure conditions were collected retrospectively. Exposure may have occurred during years to decades before the tumour occurred, thus case-control studies are particularly prone to uncertainties in the individual's recall of past job histories. Insufficient data on exposure conditions and recall bias are the major weaknesses in many of the available studies on formaldehyde. Another limitation in some nested case-control studies is the small number of cases.

However, there are also strengths of the case-control studies to be noted. To examine associations between the exposure to a substance of concern and a tumour with a long latency period that spontaneously occurred at very low percentages in the population requires extremely large sizes of cohorts to reach sufficiently high statistical power (as demonstrated for the key cohort studies, see above). In particular, for rare tumours, case-control studies are an efficient way to analyse possible associations. In contrast to cohort studies based on cancer-related mortalities, case-control studies analyses are conducted on incidences of tumours. For tumour types with a low rate of fatal outcome or long survival time since first appearance of the tumour, sensitivity of cohort studies may be limited.

Due to weaknesses in the study design, case-control studies that did not result in increased risks for a certain tumour being associated with the substance of concern could not (or could only rarely) be taken as evidence against an association. Therefore the available non-supportive case-control studies are still consistent with supportive evidence of an association of formaldehyde tumours at the site of contact.

The DS documented in Table 27 of the CLH report, several case-control studies on nasopharyngeal/pharyngeal/sino-nasal tumours that were able to detect statistically significant increases in risks that were supported by a statistically significant trend as well as further case-control studies that revealed an increase in risk that did not reach statistical significance.

RAC took note of the strengths and weaknesses of the available case-control studies during the opinion development process. It was concluded that greater weight be given to case-control studies, where an industrial hygienist assessed the exposure status than to those studies that considered ever/never exposure to formaldehyde only.

Risks for sino-nasal cancers were significantly increased in some case-control studies, additional studies revealed elevated risks, although the increases were not statistically significant. Relevant studies (where industrial hygienist had assessed exposure information), that support that the evidence of sino-nasal cancer is linked to formaldehyde exposure are the studies of Hayes (1986) and Luce (1993). Separate calculations were done on exposure assessment by two independent hygienists and revealed increased risks for squamous cell carcinomas with little/no exposure to wood dust (Hayes, 1993). Luce (1993) estimated odds ratio for squamous cell carcinomas and adenocarcinomas separately and found increased risks for sino-nasal adenocarcinomas that after adjustment for wood dust exposure was still increased, but not statistically significant (OR 8.1, 95% CI 0.9-73). The induction of squamous cell carcinomas and adenocarcinomas appears

plausible as in rodents the majority of nasal tumours were squamous cell carcinomas, adenocarcinomas and other tumour types were induced as well indicating that at the site of contact several cell types may be the origin of tumour growth.

The RAC agreed with DS who concluded that there is some evidence of a link between formaldehyde exposure and induction of sino-nasal cancer from case-control studies. DS judged the overall evidence to be insufficient to conclude on an association of formaldehyde exposure since the key cohort studies could not reproduce the finding. However, the RAC considered the absence of significant increases in nasal tumours from the three key cohort studies as not inconsistent with some evidence from case-control studies. This is mainly due to the statistical power to detect a two-fold increase at a sufficiently high level (≥80%) was poor in the key cohort studies (Hauptmann, 2003 9%-13%, Coggon, 2003 7-14%, Pinkerton, 2004 16% (BfR, 2006)). The nasal tumours in the Pinkerton study were merged with other respiratory tumours and any excess that exists could therefore be masked. In addition, some evidence came from the Danish industrial cohort study (Hansen, 1995), who found increased proportionate incidences of sino-nasal cancers in workers who worked at least 10 years before diagnosis in formaldehyde producing/using companies. Incidences remained significantly elevated after adjustment for wood dust.

Risks for NPC were increased in several case-control studies, a number of them did not show statistical significance for increased OR. RAC gave priority to the study of Vaughan (2000) on NPC cases without wood dust exposures and on which industrial hygienist classified the level of formaldehyde exposure, although it is acknowledged that there may be an overlap of NPC cases between this study and the NCI cohort study. Risks for NPC were significantly increased for jobs with probability of exposure (classified as possible, probable or definite) and significant trends for duration and cumulative exposure were seen.

Risks for carcinogenic potential at other pharyngeal sites (oro- or hypopharyngeal area) and larynx were increased in some case-control studies, but in several studies the number of cases were small or increases were not statistically significant. Significant increases of risk for hypopharyngeal cancer were seen in the study of Laforest (2000) for exposed workers with exposure probability >10% and duration above 20 years and for workers with high exposure probability.

Meta-analysis

Nasopharyngeal cancer

In the first study (Blair et al., 1990), analyzing over 30 cohort and case-control studies on the relationship between formaldehyde exposure and cancers, a non-significant excess of nasopharyngeal cancer (combined relative risk (CRR) 1.2) was observed. Relative risks for nasopharyngeal cancer by level or duration of exposure to formaldehyde on the basis of Blair et al. (1987), Roush et al. (1987) and Vaughan et al. (1986a) were: unexposed: RR = 1.0, lower level: RR = 1,1 and higher level: RR = 2,1 ($p \leq 0.05$). The authors concluded that it was likely that the excesses of nasopharyngeal cancer observed were caused by exposure to formaldehyde.

In the second study (Partanen, 1993), the relative risks for nasopharyngeal cancer from 35 cohort and case-control studies by level or duration of exposure to formaldehyde were based on the papers of Vaughan et al. (1986a), Vaughan et al. (1986b), Blair et al. (1986), Roush et al. (1987) and Hayes et al. (1990): Low-medium level or duration of exposure: RR = 1,59 (95% CI: 0,95-2,65) and substantial level or duration of exposure: RR = 2,74 (95% CI: 1,36-5,55).

The study by Collins et al. (1997) analysed 47 cohort and case-control studies related to formaldehyde exposure and used meta-analytic techniques to assess findings for cancers of the lung, nose/nasal sinuses, and nasopharynx. The analyses indicated that workers with formaldehyde exposure had essentially null findings for lung cancer and a slight deficit of sino-nasal cancer.

Nasopharyngeal cancer rates were elevated moderately in a minority of studies. Most studies, however, did not find any nasopharyngeal cancers, and many failed to report their findings. After correcting for underreporting, Collins et al. (1997) found a meta relative risk of 1.0 for cohort studies and of 1.3 for case-control studies. The review of data on exposures to formaldehyde in various studies indicated that the NPC case-control studies represented much lower and less certain exposures than the cohort studies. The authors concluded that the available studies do not

support a causal relation between formaldehyde exposure and nasopharyngeal cancer. The disagreement with the conclusions of two previous meta-analyses was primarily due to taking into consideration of the Collins et al. (1997) study, which did not report the excess of NPC risk.

The study by Bosetti et al. (2008) included all original cohort investigations published until February 2007, which provided information on formaldehyde exposure and cancer risk. These included cohort studies of formaldehyde exposed industry workers and cohort studies of professionals who used formaldehyde, such as pathologists, anatomists and embalmers.

Table 4. Standardized mortality ratio (SMR) of nasopharyngeal cancer among industry workers exposed to formaldehyde and corresponding 95% confidence intervals (CI), by study and overall (Bosetti et al. 2008)

Study – industry workers	Cancer cases	SMR	95% CI
Hauptmann et al. (2003) Plant 1	6	9,10	4,09 – 20,26
Hauptmann et al. (2003) Plant 2 - 10	2	0,64	0,16 – 2,56
Coggon et al. (2003)	1	0,50	0,07 – 3,55
Pinkerton et al. (2004)	0	0,00	0,00 – 3,00
Pooled estimate	**9**	**1,33**	**0,69 – 2,56**

This comprehensive qualitative and quantitative meta-analysis indicated that there was no appreciable excess of risk for cancers of the oral cavity and pharynx, sinus and nasal cavity and lung in the industry workers and professionals exposed to formaldehyde. The slight excess risk of nasopharyngeal cancer found in industry workers, based on 9 deaths, was due to a cluster of 6 deaths in a single plant in North America (Plant 1 of the NCI cohort). Recent evidence suggests that this cluster may be explained by prior exposure to metal working (Marsh 2007).

The meta-analysis study by Bachand et al. (2010) selected 18 cohort and case-control studies on nasopharyngeal cancer risks in populations exposed to formaldehyde. The studies have taken into account one or more of the following formaldehyde exposure indicators: exposure (yes/no or high/low/none or possible/probable); time since first exposure; peak, average, or cumulative exposure; and duration of exposure.

Table 5. Relative risk (RR) of nasopharyngeal cancer among exposed to formaldehyde and corresponding 95% confidence intervals (CI), by study and overall (Bachand et al. 2010)

Cohort studies (industry and professionals)	**RR**	**95% CI**
Stroup et al. (1986)	0,15	0,00 – 0,82
Marsh et al. (2007) Plant 2 – 10	0,42	0,02 – 8,00
Levine et al. (1984)	0,48	0,01 – 2,68
Coggon et al. (2003)	0,50	0,01 – 2,78
Pinkerton et al. (2004)	0,64	0,13 – 1,86
Marsh et al. (2005) Plant 2 – 10	0,65	0,08 – 2,33
Stern et al. (1987) Tannery B	0,88	0,29 – 2,07
Stern et al. (1987) Tannery A	1,02	0,21 – 3,01
Hauptmann et al. (2004) Plant 1 - 10	2,10	1,05 – 4,21
Marsh et al. (2007) Plant 1	4,43	1,78 – 9,13

Marsh et al. (2005) Plant 1	10,32	3,79 – 22,47
Cohort studies pooled estimate	**0,72**	**0,40 – 1,29**
Case-Control studies	**RR**	**95% CI**
Armstrong et al. (2000)	0,71	0,34 – 1,43
Gustavsson et al. (1998)	1,01	0,49 – 2,07
Roush et al. (1987)	1,27	0,91 – 1,77
Vaughan et al. (1986b)	1,27	0,60 – 2,69
Vaughan et al. (2000)	1,30	0,80 – 2,10
Hildesheim et al. (2001)	1,40	0,93 – 2,20
Marsh et al. (2007) Plant 1	3,50	0,41 – 6,31
Pooled estimate	**1,22**	**1,00 – 1,50**

Summary estimates for nasopharyngeal cancers were not elevated after excluding plant 1 with an unexplained cluster of nasopharyngeal cancers (cohort RR = 0.72, 95% CI: 0.40, 1.28). The summary estimate was increased for case-control studies overall, but the summary OR for smoking-adjusted studies was 1.10 (95% CI: 0.80, 1.50). In the opinion of the authors (Bachand et al. 2010) the previously reported association between formaldehyde exposure and NPC may have been driven by results from a single anomalous production plant and possibly uncontrolled confounding due to smoking.

Lymphohaematopoietic malignancies

In the study of NCI cohort consisting of 25 619 workers employed in 10 industrial plants (Hauptmann et al. 2003), mortality from all causes, all cancers, and all lymphohaematopoietic malignancies compared with mortality among the U.S. population was statistically significantly lower among workers, regardless of exposure status.

For unexposed workers, the SMRs for mortality from all causes, all cancers, and all lymphohaematopoietic malignancies were respectively: 0.77 (95% CI = 0.72 to 0.83), 0.65 (95% CI = 0.56 to 0.75), and 0.62 (95% CI = 0.39 to 1.00). For exposed workers, the SMRs for mortality from all cancers and all lymphohaematopoietic malignancies were respectively: 0.95 (95% CI = 0.93 to 0.97), 0.90 (95% CI = 0.86 to 0.94), and 0.80 (95% CI = 0.69 to 0.94).

In exposed workers, there were statistically significantly fewer deaths than expected from non-Hodgkin lymphoma (SMR = 0.61, 95% CI = 0.46 to 0.83), whereas there were more deaths than expected from Hodgkin disease (SMR= 1.26, 95% CI = 0.81 to 1.95), although the increase was not statistically significant. Among unexposed workers, there were statistically significantly fewer deaths than expected from leukaemia (SMR = 0.38, 95% CI = 0.14 to 1.00) and more deaths than expected from multiple myeloma (SMR =1.23, 95% CI = 0.51 to 2.95), although the increase was not statistically significant.

Although the risk of lymphohaematopoietic malignancies in the NCI cohort was not higher than in U.S. population, the authors have studied the relative risk of lymphohaematopoietic malignancies depending upon categories of constructed exposure metrics as described in the section on solid cancer above (Hauptmann et al. 2004). The internal comparisons of the relative risk of death due to lymphohaematopoietic malignancies in subpopulations of the cohort stratified according to formaldehyde exposure metrics were made. The workers assigned to the low-exposure category were used as the reference population in internal analyses for calculation of relative risks. Relative risks for leukaemia (69 deaths), particularly for myeloid leukaemia (30 deaths), increased with formaldehyde exposure. Compared with workers exposed to low peak levels of formaldehyde exposure (0.1–1.9 ppm), relative risks for myeloid leukaemia were 3.46 (95% CI =1.27 to 9.43) for workers exposed to peak levels of exposure >4.0 ppm. Compared with workers

exposed to low levels of average exposure intensity to formaldehyde (0.1–0.4 ppm), workers exposed to 0.5–0.9 ppm and >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) (also only moderate strength). The relative risk for leukaemia was not associated with cumulative exposure or with duration of exposure.

These increases in internal mortality rates (RR) due to myeloid leukaemia among workers classified by Hauptmann et al. (2003) for two exposure categories, namely peak formaldehyde exposure, and to a lesser extent, average intensity of formaldehyde exposure (AIE) were not confirmed by Marsh and Youk (2004), who have analyzed the same cohort data provided by the original authors.

For exposure category "Highest peak formaldehyde exposure" in the subgroups classified for unexposed subjects and for subjects in the lowest exposure category (>0–1.9 ppm), which NCI used as the reference population for calculation of internal RRs, the SMRs calculated by Marsh and Youk (2004) based on regional mortality rates were 0.38 (95% CI = 0.10 to 0.97) and 0.50 (95% CI= 0.28–0.81) and they were significantly lower than mortality rates for leukaemia in regional and US populations. The SMRs for leukaemia and for myeloid leukaemia in the NCI cohort calculated by the same authors for all categories and levels of formaldehyde exposure metrics (highest peak formaldehyde exposure, average intensity of exposure, cumulative exposure, duration of exposure) were all not statistically significantly different from US and regional population mortality rates. Also relative risks (RR) for leukaemia and myeloid leukaemia calculated for workers stratified according to duration of time worked in highest peak and time since first highest peak were not statistically significantly different from the internal reference subpopulations with lowest exposure.

Thus the key findings of the Hauptmann et al. study (2003) for highest peak exposure and AIE showing an increase in RR due to exposure to formaldehyde, were due to choosing as internal reference populations the sub-cohorts of workers with mortality due to leukaemia and myeloid leukaemia much lower than in the regional and US populations.

The latest update of the NCI cohort study (Beane Freeman et al., 2009) confirmed that mortality due to all lymphohaematopoietic malignancies, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, leukaemia, lymphatic leukaemia and myeloid leukaemia were not different from US population. The relative risks for leukaemia and myeloid leukaemia were not different in various exposure metrics categories (highest peak formaldehyde exposure, average exposure intensity, cumulative exposure). Thus the findings of Hauptmann et al. (2003) in the earlier update study of the same cohort on the increased relative risk of death due to myeloid leukaemia in the exposure categories (highest peak formaldehyde exposure, average exposure intensity) were not confirmed. The extension of the observation period of the cohort resulted in lowering risk of myeloid leukaemia and leukaemia in these exposure categories.

The findings of Beane Freeman et al. (2009) on lack of increased SMR for leukaemia and myeloid leukaemia are supported by the results of studies of industrial workers in British cohort (Coggon et al. 2003) and in the NIOSH cohort (Pinkerton et al. 2004), which did not show an increase in standardised mortality ratios for lymphohaematopoietic malignancies and Hodgkin lymphoma.

On the other hand, this study (Beane Freeman et al. 2009) revealed statistically significant increased relative risks within internal comparisons within cohort for the highest versus lowest peak formaldehyde exposure category (≥4 ppm versus >0 to <2.0 ppm) for all lymphohaematopoietic malignancies (RR = 1.37; 95% CI = 1.03 to 1.81, p-trend =0.02) and for Hodgkin lymphoma (RR = 3.96; 95% CI = 1.31 to 12.02, p-trend =0.01).

Regarding meta-analysis data on lymphohaematopoietic malignancies, in the study of Blair et al. (1990), over 30 reports from cohort and case-control studies on formaldehyde were analysed. These reports have focused on professional groups such as funeral directors and embalmers, anatomists, pathologists, and workers in formaldehyde facilities producing formaldehyde, resins, plastic molding, decorative laminates, plywood, particle board, and apparel.

Among professionals, significant excesses occurred for leukaemia (Combined Relative Risk (CRR) 1.6, 11 of the 13 investigations showing excesses ranging from 1.1 to 3.1).

In contrast to professionals, industrial workers did not show elevated mortality from leukaemia (CRR 1.1). According to authors the lack of excess of leukaemia among industrial workers would seem to indicate that formaldehyde is not contributing to the excess of these tumours.

In the study of Collins and Linker (2004), twelve cohort studies, four proportionate mortality ratio (PMR) or four proportionate incidence ratio (PIR) studies, and two case-control studies were selected for meta-analysis because they were found to examine leukaemia rates and potential formaldehyde exposure. They used standardized mortality ratios (SMR) for the cohort studies, the PMRs for the PMR studies and the relative risks (RR) from the case-control studies to examine increased leukaemia rates among formaldehyde exposed workers. The studies include a wide range of potential formaldehyde exposure including tissue preservation (embalmers, pathologists, and anatomists), garment making, formaldehyde monomer production, core making in foundries, and other industrial applications such as plastic resins production. Table 5 provides selected details of the studies used in the analysis.

Table 5. Meta-relative risk of leukaemia for various type of studies (Collins and Linker 2004)

Type of study	Number of studies	Number of leukaemias	Meta-relative risk	95% confidence intervals
Cohort	12	174	1,0	0,9 – 1,2
PMR or PIR	4	106	1,2	1,0 – 1,5
Case-control	2	7	2,4	0,9 – 6,5
All studies	18	287	1,1	1,0 – 1,2

The possibility that inhaled formaldehyde may induce distant-site toxicity, including developmental toxicity (Collins et al., 2001b), hepatotoxicity (Beall and Ulsamer, 1984), and cancers distant from the respiratory tract (Soffritti et al., 1989) have been investigated. However, no conclusive evidence has been reported for distant-site toxicity (Liteplo and Meek, 2003) and a substantial body of evidence has been reported from studies in experimental animals and humans that argues against this possibility (Dallas et al., 1992; Heck and Casanova, 1990, 2004; Pross et al., 1987; Til et al.,1989; Woutersen et al., 1987).

The study of Bosetti et al. (2008) included all original cohort investigations published until February 2007, which provide information on formaldehyde exposure and cancer risk. These included cohort studies of formaldehyde-exposed industry workers and cohort studies of professionals who used formaldehyde, such as pathologists, anatomists and embalmers.

Relative risks for lymphatic and haematopoietic cancer are presented in Table 6 and relative risks for leukaemia in Table 7.

Table 6. Relative risk (RR) of lymphatic and haematopoietic cancer among industry workers exposed to formaldehyde and corresponding 95% confidence intervals (CI), by study and overall (Bosetti et al. 2008)

Industry workers	**Cancer case**	**RR**	**95% CI**
Bertazzi et al. (1989)	7	1,43	0,68 – 3,00
Andjelkovich et al. (1995)	7	0,59	0,28 – 1,24
Hauptmann et al. (2004)	161	0,80	0,69 – 0,93
Pinkerton et al. (2004)	59	0,97	0,75 – 1,25
Pooled estimate	**234**	**0,85**	**0,74 – 0,96**
Professionals			

Harrington and Shannon (1975)	8	2,00	1,00 – 4,00
Harrington and Shannon (1975)	3	0,55	0,18 – 1,71
Walrath and Fraumeni (1983)	25	1,21	0,82 – 1,79
Walrath and Fraumeni (1984)	19	1,22	0,78 – 1,91
Levine et al. (1984)	8	1,24	0,62 – 2,48
Stroup et al. (1986)	18	1,20	0,76 – 1,90
Hayes et al. (1990)	115	1,39	1,16 – 1,67
Hall et al. (1991)	10	1,44	0,77 – 2,68
Matanoski (1991)	57	1,25	0,96 – 1,62
Pooled estimate	**263**	**1,31**	**1,16 – 1,47**

Table 7. Relative risk (RR) of leukaemia among industry workers exposed to formaldehyde and corresponding 95% confidence intervals (CI), by study and overall (Bosetti et al. 2008)

Industry workers	**Cancer case**	**RR**	**95% CI**
Andjelkovich et al. (1995)	2	0,43	0,11 – 1,72
Coggon et al. (2003)	31	0,91	0,64 – 1,29
Hauptmann et al. (2004)	65	0,85	0,67 – 1,08
Pinkerton et al. (2004)	24	1,09	0,73 – 1,63
Pooled estimate	**122**	**0,90**	**0,75 – 1,07**
Professionals			
Harrington and Shannon (1975)	1	0,63	0,09 – 4,47
Harrington and Shannon (1975)	1	0,45	0,06 – 3,19
Walrath and Fraumeni (1983)	12	1,40	0,80 – 2,46
Walrath and Fraumeni (1984)	12	1,75	0,99 – 3,08
Levine et al. (1984)	4	1,60	0,60 – 4,26
Stroup et al. (1986)	10	1,50	0,81 – 2,79
Hayes et al. (1990)	24	1,57	1,05 – 2,34
Hayes et al. (1990)	7	0,74	0,35 – 1,55
Hall et al. (1991)	4	1,52	0,57 – 4,05
Matanoski (1991)	31	1,35	0,95 – 1,92
Pooled estimate	**106**	**1,39**	**1,15 – 1,68**

For lymphoid neoplasms and leukaemia there were excess risks among pathologists and other professionals, whereas the overall RRs were, if anything, below unity in industry workers. This indicates that other occupational or lifestyle characteristics of pathologists, anatomists and

embalmers, rather than formaldehyde, are likely to be the underlying factors associated with the excess risk of these neoplasms among these professionals.

In the study of Bachand et al. (2010) (Table 8) a total of 283 abstracts were screened, and 129 were excluded because the study: (1) was not an epidemiological study; (2) did not focus on formaldehyde; (3) focused on an outcome other than cancer; or (4) did not present results for NPC or leukaemia. From these 154 articles, the authors next excluded commentaries, review articles, and any articles that did not reach the criteria after more detailed review. Seventeen studies of leukaemia and 18 studies of nasopharyngeal cancers were included in the final meta-analyses, respectively. The studies included investigated one or more of the following formaldehyde exposure indicators: exposure (yes/no or high/low/none or possible/probable); time since first exposure; peak, average, or cumulative exposure; and duration of exposure.

Table 8. Relative risk (RR) of leukaemia among exposed to formaldehyde and corresponding 95% confidence intervals (CI), by study and overall (Bachand et al. 2010)

Cohort studies (industry and professionals)	**RR**	**95% CI**
Andjelkovich et al. (1995)	0,43	0,05 – 1,57
Harrington and Shannon (1975) (lab techs)	0,45	0,01 – 2,53
Robinson et al. (1987)	0,59	0,02 – 14,67
Harrington and Shannon (1975) (pathologists)	0,63	0,02 – 3,48
Stern et al. (1987) (Tannery B)	0,75	0,28 – 1,64
Stern et al. (1987) (Tannery A)	0,77	0,21 – 1,97
Marsh et al. (2004)	0,79	0,62 – 1,01
Coggon et al. (2003)	0,91	0,62 – 1,29
Stellman et al. (1998) (RR)	0,96	0,54 – 1,71
Beane Freeman et al. (2009)	1,02	0,85 – 1,22
Pinkerton et al. (2004)	1,09	0,70 – 1,62
Wong (1983)	1,18	0,13 – 4,26
Matanoski (1991)	1,35	0,92 – 1,92
Stroup et al. (1986)	1,50	0,70 – 2,70
Hall and Harrington (1991)	1,52	0,41 – 3,89
Levine et al. (1984)	1,60	0,44 – 4,10
Pooled estimate	**1,05**	**0,93 – 1,20**

Among industrial workers, an increased leukaemia risk was not seen in any study published before or after 1995. The consistent findings of no association between exposure and leukaemia among formaldehyde-exposed industrial workers over time do not support a causal association with formaldehyde. Differences between professional and technical workers (who are likely to be exposed to lower levels of formaldehyde) and industrial workers cannot be explained by the current studies.

This meta-analysis (Bachand et al., 2010) on formaldehyde exposure and leukaemia demonstrates there is little consistent evidence of a relationship, and that the overall increased risk previously reported was driven by PMR (Proportionate Mortality Ratio) studies.

In conclusion, while some studies have found increased rates of leukaemia, the epidemiology data do not show consistent findings across studies for leukaemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukaemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation.
Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukaemia.

Classification criteria

According to the CLP Regulation for the purpose of classification for carcinogenicity, substances

are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard (Section 3.6.2.1. of the Guidance on the Application of the CLP Criteria).

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories (Section 3.6.2.2.3.):

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

In establishing a causal relationship the following criteria have been considered to analyse strength of this relationship:

1. Strength of association

The strength of association can be measured e.g. based on the magnitude of standardized mortality ratio, relative risk or odds ratio. However, small increases in these relative frequency estimators do not exclude the existence of a causal relationship.

The main evidence for an association between formaldehyde exposure and NPC comes from the NCI study (Hauptmann, 2004). Significant increases in NPC-related mortalities occurred in exposed workers compared to the general population, and a significant dose-response relationship for high peak exposure and cumulative exposure was observed, although there may be additional uncertainty in the NCI cohort findings because of small sample bias and case ascertainment issues.

Supporting evidence comes from other studies on the plant 1 cohort, which is part of the NCI study, although the discrepancy between the findings for plant 1 and the other plants was noted (Marsh, 2002, Marsh et al. 2007a).

Supporting evidence also comes from case-control studies (in particular Vaughan, 2000), although it is acknowledged that there may be an overlap in case ascertainment with the NCI study.

The accumulation of five NPC in one plant of the NCI study gave rise to uncertainty, especially in relation to the small number of cases involved:

- An update on the NCI study is expected that will give information on the corrections for missing deaths. This update may or may not affect the significance of the peak and cumulative exposure-related NPC. Noting the effect that resulted from the update of haematopoietic cancer (Beane-Freeman et al., 2009) full reliance cannot be placed on the trend statistics on NPC.
- Some uncertainties remain on the accumulation of NPC in plant 1.
- Available post-hoc re-analyses on plant 1 did not identify any other plausible cause of NPC.

Other tumours (sino-nasal, other pharyngeal, laryngeal): Some, overall weak evidence comes from some case-control studies (e.g., Hansen, 1995). Mainly due to small data base and poor exposure estimations, other studies (including cohort studies) were not informative.

Evidence on an association between formaldehyde exposure and leukaemia and myeloid leukaemia remains questionable.

2. Consistency

High consistency of results of various epidemiological studies could be inferred if different study designs, studies of different populations at different locations would provide repeatable effects in terms of type of tumours induced and their location.

Increased NPC-related mortalities in the NCI study were not confirmed by the Coggon (2003) and the Pinkerton (2004) studies. Due to the rarity of NPC in the normal population, sizes of both cohorts were too small to be sensitive enough to detect a 2-fold increase in tumour-related mortalities at a sufficiently high power. Therefore, the lack of positive outcome is not inconsistent with the results of Hauptmann (2004). It is to be noted that the Coggon (2003) study revealed a small, but not significant increase in pharyngeal tumours.

The results of the positive cohort studies demonstrate consistency with some of the case-control studies. In particular, the higher quality study gave supportive evidence.

3. Dose-response relationship

In the NCI study, a strong dose-response relationship was seen for peak-exposure and cumulative exposure. All seven cases were in the high peak exposure group and the trend was highly significant.

Quantitative exposure assessment was generally absent from the case-control studies. An exposure-response relationship was also seen in higher-quality studies where exposure categorization was conducted by industry hygienists.

4. Plausibility

While the mechanism of induction of nasopharyngeal cancer is biologically plausible as a local direct effect of formaldehyde, leading to intensive regenerative cell proliferation and mutagenic effects, which may lead to initiation of the tumour, the mechanism of induction of lymphohaematopoietic malignancies is uncertain and not biologically probable due to the toxicokinetics of formaldehyde.

Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry.

5. IARC evaluation

In IARC's re-assessment of formaldehyde (IARC, 2012), a strong association between exposure to formaldehyde and NPC from the NCI study is noted and positive associations were also observed in case-control studies, in particular those of larger sizes and higher-quality exposure assessments. IARC concluded that formaldehyde causes NPC in humans. In was considered unlikely that confounding or bias could explain the observed association.

With respect to sino-nasal tumours, IARC noted that many case-control studies show positive associations for exposure to formaldehyde and sino-nasal cancer, some with evidence of an exposure-response pattern. IARC concluded that residual confounding could not be ruled out in the case-control studies and noted the discordant results between the cohort and case-control studies.

IARC concluded – on balance – that the epidemiological evidences from two cohort studies and from studies of professionals and from a nested control study shows that occupational exposures to formaldehyde causes leukaemia. Its previous re-assessment of 2004 was published before the update on the NCI study was published (Beane Freeman et al., 2009), which demonstrated lack of increased SMR for leukaemia and myeloid leukaemia.

Comparison with classification criteria

The RAC is of the opinion that existing evidence is not sufficient for classifying formaldehyde to category **Carc. 1 A** according to CLP criteria and according to Directive 67/548/EEC because the available human evidence of carcinogenicity is not sufficient and a causal relationship has not been established between exposure to the agent and human cancer with sufficient confidence.

- A positive association has been observed between exposure to formaldehyde and the frequency of nasopharyngeal cancers in one industrial cohort for which a causal interpretation is considered to be plausible, but some uncertainties remain and chance, bias or confounding could not be ruled out with reasonable confidence. Supporting evidence comes from case-control studies.
- There is strong evidence from animals, evidence from one cohort study and some supporting evidence from case-control studies. In its conclusion on the overall strength of evidence, the RAC took into account the remaining uncertainties.

In the opinion of the RAC the data presented in the background document warrant classification of formaldehyde as **Carc. 1B** according to the CLP criteria (Carc. Cat. 2; R45 according to Directive 67/548/EEC) for the following reasons:

- There is **limited evidence of carcinogenicity in humans** mainly from the positive association of nasopharyngeal tumours in industrial cohorts.

  The CLP guidance notes on this situation '*The quality and power of epidemiology studies require expert consideration and would normally lead to a Category 1A classification if data of adequate quality shows causality of exposure and cancer development. Where there is sufficient doubt in the human data then classification in Category 1B may be more appropriate*.

  'Taking into account the significant, but overall small increase in tumours and considering the remaining uncertainties, RAC considers that the strength of evidence is not sufficient to justify classifying in carcinogenicity category 1A.
- There is **sufficient evidence of carcinogenicity from animal studies** to conclude that formaldehyde is a presumed human carcinogen.

  The CLP guidance defines sufficient evidence of carcinogenicity in animals as: '*a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under GLP, can also provide sufficient evidence.'*

  Several studies in both sexes of three strains of **rats** demonstrated a dose-related increase in nasal tumours of the upper respiratory tract following chronic inhalation exposure. Squamous cell carcinomas and other less differentiated malignancies were observed at concentrations of ≥ 6 ppm, and benign squamous cell tumours were seen at 2 ppm. Nasal tumours were not seen in any of the internal control groups of the animal studies. The spontaneous incidence of nasal tumours and in particular of squamous cell tumours is very low.
- The database on **mice** is small, but gives some evidence of carcinogenic potential in the mouse nasal region. The only available inhalation study in mice demonstrated similar lesions identified in rats as precursor lesions in tumour development. The predominant tumour type in rats was also seen in mice, albeit at lower incidences (2/17 animals) than observed in rats at the same concentration. Mice are assumed to be less sensitive than rats (due to stronger reduction in their minute volume). However, the database for this species and for animals exposed for longer than 18 months is very limited.
- Data on the **hamster** are even more limited, the only information coming from one dose group from a chronic study, which revealed precursor lesions similar to those seen in rats. However, this study is considered invalid for assessment of carcinogenicity, as only macroscopically dense areas were examined microscopically.
- Formaldehyde is **genotoxic in somatic cells at the site of contact**. Due to its high reactivity, particularly DPX were induced in the nasal mucosa of rats and monkeys that were exposed by inhalation. DPX can be induced in proliferating and non-proliferating cells. In proliferating cells, unrepaired DPX can lead to mutagenic effects. The potential to cause mutagenic effects has been demonstrated in vitro. The substance induced **clastogenic effects** (chromosomal effects such as chromosomal aberrations, micronuclei and sister

chromatid exchanges) as well as **genotoxic effects** (DPX and DNA adducts) in mammalian cells lines as well as in human cells lines. It is concluded that formaldehyde is a local acting genotoxic carcinogen.

- The common understanding (also proposed by the Dossier submitter) is that formaldehyde causes tumours above a threshold concentration by mechanisms that are initiated by the cytotoxic effect and secondarily increase regenerative cell proliferation. It is worth noting that a threshold for induction of cell proliferation has not been identified. A recent cell proliferation study demonstrated a linear dose-response for cell proliferation that calls the previous interpretation on the existence of a practical threshold into question. Equally, no clear threshold has been identified for DPX formation, and dose-related increases were also seen below 2 ppm and although assumed to be the case, it remains unknown whether DPX formation below 2 ppm will fully be repaired. While the absence of micronuclei in nasal cells of volunteers under strictly controlled short-term exposure conditions at a concentration of 0.7 ppm (Zeller et al., 2011) indicated that mutagenicity may not occur secondary to DPX formation, these results were not consistent with a number of positive studies that found micronuclei in buccal/nasal cells at concentrations below 2 ppm, albeit at less well documented exposure conditions. The database is not sufficient to demonstrate that cytotoxicity/cell proliferation is the only initial event or whether cytotoxicity, increased cell proliferation and DPX formation run in parallel.

  Overall, the database for low-dose effects is limited. The fact that the responses of key events below 2 ppm are non-significant, albeit dose-related, may lead to consideration of the possibility of a threshold mode of action. However, the data **does not allow a firm conclusion on a threshold-mode of action** or the identification of a threshold. Extrapolation from 2 ppm formaldehyde to lower concentrations may be linear or non-linear and no firm conclusion whether the carcinogenic response is primarily caused by a genotoxic or a cytotoxic mechanism is possible.

- The **difference in sensitivity among species** to formaldehyde-induced tumours correlates with differences in sensitivity to cytotoxic and regenerative lesions, as shown for the rat and mouse. Lesions of similar nature to those seen in rats (and other species) were also induced in monkeys and were considered as relevant for humans. Lesions and increased cell proliferation in the monkey were not confined to the nose and extended to more distal parts of the respiratory tract. Differences in the distribution among species were related to anatomical and airflow differences and can be interpreted as supportive for identifying the nasopharyngeal region as one target area in humans.

- The evidence of a presumed human carcinogen is strengthened by the **coincidence of tumours** occurring **at the site of first contact** in rats and humans.

- **Equivocal evidence on a carcinogenic effect at other sites of contact** after prolonged oral exposure was provided in the dossier. The most valid study did not indicate a tumour response in the gastrointestinal tract, while another study with shorter duration found such tumours.

  No conclusion on carcinogenicity can be drawn for the dermal route due to the lack of data.

- Limiting the classification to the inhalation route and hence use of route-specific hazard statements (e.g., H350i (CLP), R49 (DSD)) is not warranted, as formaldehyde is absorbed via oral and dermal exposure and available data are insufficient to demonstrate absence of carcinogenic potential for routes other than inhalation.

- Besides the findings of carcinogenicity in the upper respiratory tract, the concern from human data on tumours in the lymphohaematopoietic system were not supported by animal data. A sufficient number of organs were examined in only one study (Kerns et al., 1983). In addition, the NALT has been examined in a retrospective study and did not give indications of tumour development at distant sites or at the site of contact.

The RAC is of the opinion that existing evidence does not warrant classifying formaldehyde as **Carc. 2** according to CLP criteria and according to Directive 67/548/EEC to Carc. Cat. 3 because

- Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in

animals do not meet any of the criteria of 3.6.2.3.1 CLP guidance, which require Carc. 2 if there is:

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

In cases where there is only information from animal studies, the evaluation of animal carcinogenicity data requires consideration of additional factors which may increase or decrease the level of concern for human carcinogenicity and the classification category. Annex I, 3.6.2.6 a-k of the Guidance on the Application of the CLP Criteria includes considerations on modes of **non-genotoxic** mechanisms of action, e.g. when the identified mode is not relevant for humans or a secondary mechanism of action with the implication of a practical threshold above a certain dose level exists (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation), which may lead to a downgrading of a Category 1 to Category 2 classification.

The general criteria for Carc. 2 are not met for formaldehyde. Evidence on formaldehyde's carcinogenicity is not limited to animal data and thus the specific factors of 3.6.2.6 a-k are not to apply. Furthermore, a downgrading to Carc. 2 would also not be appropriate because the mode of action is not solely non-genotoxic.

In the opinion of the RAC, formaldehyde should be as carcinogen Carc. 1B, H350: May cause cancer (according to CLP criteria, and as Carc. Cat. 2; R45 according to Directive 67/548/EEC). The route(s) of exposure should not be stated in the hazard statement as it is not proven that other routes besides inhalation can be excluded.

References (in addition to the Background Document)

Andersen ME, Clewell HF, Bermudez E, Dodd DE, Willson GA, Campbell JL, Thomas RS (2010) Formaldehyde: Integrating dosimetry, cytotoxicity, and genomics to understand dose-dependent transitions for an endogenous compound. Toxicological Sciences 118:716-731.

Andersen ME, Clewell HF, Bermudez E, Willson GA, Thomas RS (2008) Genomic structures and dose-dependent transitions in nasal epithelial responses to inhaled formaldehyde in the rat. Toxicological Sciences 105:368-383.

Barker S, Weinfeld M, Murray D (2005) DNA protein crosslinks: their induction, repair, and biological consequences. Mutat Research 589:111-135

Checkoway H, Boffetta P, Mundt DJ, Mundt KA (2012) Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukaemia and other lymphohematopoietic malignancies. Cancer Causes Control 23:1747-1766

EPA (2010) IRIS TOXICOLOGICAL REVIEW OF FORMALDEHYDE – INHALATION. In Support of Summary Information on the Integrated Risk Information System (IRIS)
http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=223614

Greenland S, Schwartzbaum JA, Finkl WD (2000) Problems due to Small Samples and Sparse Data in Conditional Logistic Regression Analysis. Am J Epidem 151:531-539

IARC (2012) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
Volume 100F, p. 401-430
http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-29.pdf

Kuper FC (2007 formaldehyde and NALT. Formaldehyde International Science Conference, Barcelona 20-21 September 2007
http://www.formaldehyde-europe.org/fileadmin/formaldehyde/PDF/Kuper_NEW_PP_formaldehyde_NALT_Barcelona_Sept.pdf

Kuper FC (2012) Local lymphoid tissues and formaldehyde. 2nd International Formaldehyde Science Conference, 19-20 April 2012, Madrid
http://www.scribd.com/doc/91978329/Local-Lymphoid-Tissues-and-Formaldehyde-by-Frieke-Kuper

Marsh GM (2012) see Bolt HM, Morfeld P (2012) New results on formaldehyde: the 2nd International
Formaldehyde Science Conference (Madrid, 19–20 April 2012) Archives of Toxicology, 2012 Nov 9 (Epub) DOI 10.1007/s00204-012-0966-4, Presentation slides are available online via http://www.formacare.org/about-formaldehyde/science/formaldehyde-science-conference

Siew SS, Kauppinen T, Kyyrönen 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 Management and Research 4:223-232

Shangina et al. (2006) Shangina O, Brennan P, Szeszenia-Dabrowska n, Mates D, Fabianova E, Fletcher T, t'Mannetje A, Boffetta P, Zaridze D (2006) Am J Epidem 164: 367-375

Swenberg JA, Kerns WA, Mitchell RI, Gralla EJ, Pavkov KL (1980) Induction of squamous cell carcinomas of the rat nasal cavity y inhalation exposure to formaldehyde vapor. Cancer Res **40**:3398-3402.

Woutersen R (2007) Indications for leukaemia and lymphoma in former animal studies. Formaldehyde International Science Conference, Barcelona 20-21 September 2007

http://formaldehydeeurope.com/fileadmin/formaldehyde/PDF/Woutersen_formaldehyde_leukaemia.pdf

ANNEXES

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by the RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and the RAC (excluding confidential information).

Appendix

Relevant text passages of a range of comments received during public consultation on carcinogenicity (human data)

Member States Competent Authorities

Denmark:

"The classification with Carc. 1A H350 is convincingly documented in the CLH proposal.

There is sufficient human evidence for the proposed classification from the association to the nasopharyngeal cancer from occupational formaldehyde exposure. The plausibility of considering formaldehyde as a site of contact carcinogen is further supported by animal inhalation data showing nasal cancer at low levels of formaldehyde exposure."

Germany: "Considering the database on formaldehyde toxicology, Germany strongly supports this CLH proposal to classify formaldehyde (CAS 50-00-0) as Muta. 2 - H341 and Carc. 1A – H351 according to CLP regulation."

Malta: "Malta believes that the current classification of formaldehyde, that is CMR 2 under CLP, should be maintained. It is our belief that the review of available epidemiological cohorts does not unequivocally link formaldehyde exposure to nasopharyngeal cancer and therefore it is our that classification as carcinogen cat. 1A is not warranted. We are of the opinion that the basic animal and mechanistic data, which have not changed since the evaluation under the DSD, justifies only a classification to category 3 / 2 (CLP)."

Poland: "The proposed classification as Carc. 1A as presented in the CLH Report is based on nasopharyngeal cancers in humans. However there are a number of doubts such as lack of precise or previous exposure measurement, not taking into account several confounding factors or previous employment. Formaldehyde should be considered as a specific carcinogen with threshold activity."

Sweden: "SE supports classification of Formaldehyde (CAS No 50-00-0) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations."

The Netherlands: "There is a significant increase in nasopharynx tumours in both cohort and case-control studies. However, the existence of a grouping in plant 1 of the NCI cohort raises doubts on potential confounders. The NL MSCA does agree that this may be explained by the largest number of subjects exposed to peaks in this specific plant. However, the difference in the number of subjects with peak exposure in plant 1 compared to the other plants is only small and does not fully explain the grouping. We propose to include a table in the CLH report containing the number of subjects with peak exposure and the number of subjects with nasopharynx tumours to get a better overview on this issue. At the moment, the concentration of cases in plant 1 cannot be fully explained. The limited size of the best cohort study and the limited correction for residual confounding by smoking does not add to the confidence in the results. Clearly more independent cohort studies are needed. In conclusion, the epidemiological evidence is limited and confounding cannot be ruled out with sufficient confidence. Therefore, we consider that there is only limited human evidence … Overall, we consider that classification as Carc. 1B is warranted based on the criterion that on a case-by-case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals."

ENVIRON, on behalf of Momentive Specialty Chemicals UK Limited:

"The strength of the epidemiological and toxicological evidence for nasopharyngeal cancers fails to support elevating formaldehyde from a Category 2 to a Category 1A carcinogen."

American Chemistry Council's Formaldehyde Panel (ACC):

"The available human epidemiology data do not support a causal relationship between FA exposure and induction of nasopharyngeal cancer (NPC) and do not correspond to sufficient evidence of carcinogenicity in humans as required for a Carc 1A classification for the reasons listed below:

The extensive reanalyses of the National Cancer Institute (NCI) 2004 data on NPC (Marsh and Youk, 2005; Marsh, 2007a) that revealed mis-specified and non-robust internal analysis of the NCI data (i.e., NCI's results were driven heavily by anomalous findings for NPC in Plant 1 and NCI neither recognized nor properly accounted for this considerable heterogeneity or interaction structure in the NPC results across the 10 NCI study plants).

The absence of an NPC excess in the large British and NIOSH cohort studies (Coggan et al., 2003; Pinkerton et al., 2004).

The absence of a statistically significant association with FA exposure and NPC in an independent study of NCI's Plant 1 (Marsh et al., 2007b).

The finding in a nested case-control study that the NPC excess in Plant 1 of the NCI study may be related to previous employment in the nearby ferrous and non-ferrous metal working industries (Marsh et al., 2007b).

The recent reviews and meta-analyses that confirmed the absence of epidemiological evidence suggesting a causal association for FA exposure and NPC (Chang and Adami, 2006; Bosetti et al., 2007; Duhayon et al., 2008; Bachand et al., 2010).

A detailed evaluation of the impact of missing deaths in the 1994 update (Marsh et al., 2010) that points out the fact that the 1994 NCI risk estimates for NPC are incorrect, as they do not account for the change in person-year counts and possible counts of observed deaths stemming from incomplete follow-up.

Because of the current errors in the 1994 NCI cohort data, all evaluations of NPC related to formaldehyde exposure, including the CLH Report, must be re-evaluated based on corrected data from the 2004 update of the NCI study. NCI's publication describing the NCI update on morality from solid tumours, including NPC, which would allow for such re-evaluations, is in internal NCI review and pending journal submission.

Given the imminent release of the NCI update and the questions raised in the scientific literature, no classification decision should move forward without considering this publication updating the NCI cohort. Therefore, ACC concludes that ECHA should maintain the existing classification, cat 2 or cat. 3 DSD."