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PhD in Occupational and Environmental Health and Industrial Hygiene
XXIII cycle

Formaldehyde Risk Assessment: proposal of exposure limits, characterisation of exposure, and development of scenarios

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Academic year 2009/10

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List of acronyms

VOCs	Volatile Organic Compounds
HPVCs	High Production Volume Chemicals
UFFI	Urea-Formaldehyde Foam Insulation
ETS	Environmental Tobacco Smoke
OQAI	Indoor Air Quality Observatory (French)
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
LOAEL	Lowest Observed Adverse Effects Level
NCI	National Cancer Institute
CLP	Classification, Labelling and Packaging
ECHA	European Chemicals Agency
MSC	Member State Committee
IARC	International Agency for Cancer Research
NTP	National Toxicology Program
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
IPCS	International Programme on Chemical Safety
CSAF	Chemical Specific Assessment Factor
PBT	Persistent Bioaccumulative Toxic
vPvB	very Persistent very Bioaccumulative
TWA	Time Weighted Average
CMS	Chip Measurement System
RMMs	Risk Management Measures
PCA	Principle Component Analysis
ACGIH	American Conference of Industrial Hygienists
TLV	Threshold Limit Value
TNO	Netherlands Organisation for Applied Scientific Research
CEFIC	European Chemical Industry Council

ppm	Part per million
ppb	Part per billion
RELs	Reference Exposure Limits

Introduction

1.1 Key properties and applications

Formaldehyde [methanal, CAS No. 50-00-0; EC No. 200-001-8] is an organic compound with the formula CH_2O. At room temperature, it is a gas with a strong chemical reactivity (as it is electrophile) and it readily converts to derivative compounds. It has a molecular weight of 30.03, and a boiling point of -19℃ (Lide, 2003). Because of its low boiling point it is not considered to belong to the Volatile Organic Compounds (VOCs), and is not sampled or analysed with the methods used for the VOCs. As the simplest aldehyde, it is a common precursor to many other chemicals, especially polymeric compounds.

Formaldehyde does not accumulate in the environment, because it undergoes photolysis within a few hours by sunlight or biologic breakdown by bacteria present in soil or water.

It is generally commercialised as formalin, a colourless aqueous solution, with a characteristic pungent odour. Saturated solution of formaldehyde (about 40% by volume or 37% by mass) in water, usually contain a small amount of stabilizer (i.e. methanol) to limit oxidation and polymerization.

Formaldehyde ranks among leading HPVCs (High Production Volume Chemicals): in 2004 its production in EU and Norway amounted to 10.7 million tons (FormaCare, 2008) while world production was reported to be about 21 million tons (IARC, 2006). Formaldehyde is one of the most utilised chemical substances in the world as it is a common component of a large variety of materials. Because of its high versatility,

formaldehyde has application in numerous uses. Thermosetting polymers are resins that achieve hardiness through the formation of a 3-D network of bonds (curing process). Production of formaldehyde resins accounts for more than half of formaldehyde consumption and probably its most significant economic sector. The most widespread formaldehyde-based resins are:

- urea-formaldehyde,
- melamine-formaldehyde,
- phenol-formaldehyde;

Formaldehyde-based materials are employed in a huge number of products, in particular are basic components of wood-based material such as plywood, fibreboard, particle board. They are also present in adhesives, insulating foams, glues, automotive equipment, textile treatments, and dozens of other consumer's products.

Formaldehyde is also extensively used as preservative, biocide and disinfectant. Formalin is the most common solution to fix and preserve biologic specimens: hospitals, laboratories, embalmers consume significant amounts of formalin every day. In a more diluted solution, formaldehyde is also present in many household products such as detergents, disinfectants and varnishes.

1.2 Sources of exposure

Formaldehyde emerged as the first modern, non-industrial, indoor air quality issue. During 1970's when concerns about energy efficiency led to efforts to improve home insulation, Urea-Formaldehyde Foam Insulation (UFFI) became an important insulation product for existing houses. Formaldehyde-based materials have the characteristic of slowly releasing molecules of formaldehyde into the environment (see figure 1.2 Urea-formaldehyde resin structure) by hydrolysis. Indoor air surveys soon detected formaldehyde releases also from chipboards and plywood, both widely used in building and furnishing materials.

Household products such as detergents and disinfectants are also significant domestic sources of formaldehyde; among considerable indoor sources there are other consumer products like paints, adhesives, carpets, varnishes, textiles and so on.

Formaldehyde is also a by-product of combustion processes, Environmental Tobacco Smoke (ETS) in particular. Air chemistry of terpenes, contained in fragrances and air fresheners, which are more and more widespread in domestic settings, can form formaldehyde in presence of ozone (even if it is present at levels of ppb) (ECA-IAQ, 2007).

Because of its multitude of indoor sources, formaldehyde is found ubiquitously in almost all indoor environments at levels which exceed the outdoor concentrations by an order of magnitude or more. Background levels of formaldehyde present in outdoor air (in rural areas) are usually lower than 10 $\mu g/m^3$ or 8 ppb.(1 ppb = 1.24 $\mu g/m^3$).

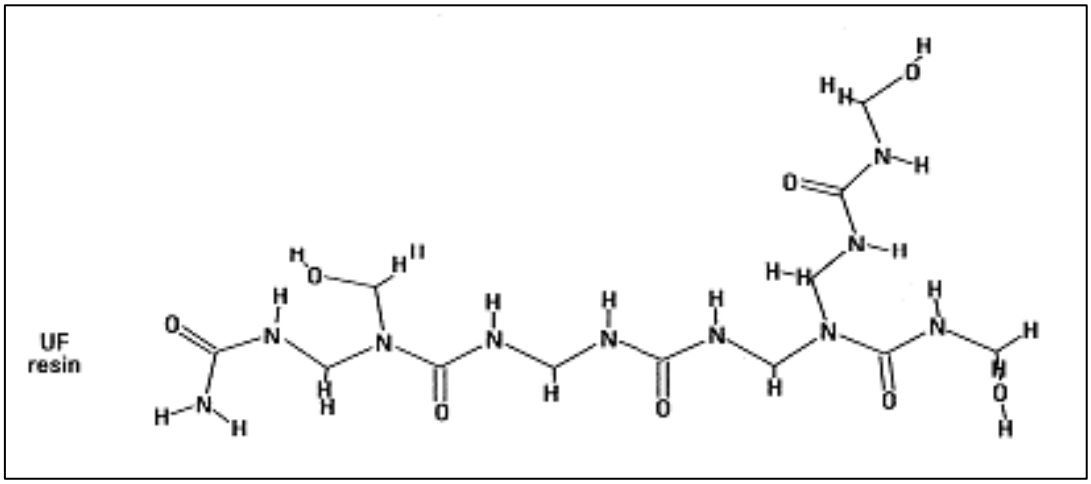
Nowadays formaldehyde emissions from wood-based panels have been regulated in most developed countries. Typical indoor levels in dwellings and offices are in the range of 15÷50 $\mu g/m^3$ (12-40 ppb), even if in some cases they can reach concentrations above 100 $\mu g/m^3$ (80 ppb) (Kotzias et al, 2005). Higher concentrations are found in environments where there is a large presence of wood-based materials, in brand new, renewed/refurnished environments or in those characterised by poor ventilation, high relative humidity and temperature.

The maximum values measured indoors varied quite a lot since the 1980s, as can be seen when comparing the various surveys carried out in Germany (GerES 1985/86) to the most recent ones from France (OQAI, Indoor Air Quality Observatory, Kircher et al, 2006) and AIRMEX (Kotzias et al, 2009). A trend to decreasing concentration over time seems to be observed. This reduction can be partially attributed to the less emitting materials being developed over time, in the context of various labelling schemes in place in different European countries, including Italy (i.e. class E1, where concentrations at equilibrium state must not exceed 0.1 ppm) where have become mandatory in 2008. Nevertheless, in spite of the restrictions adopted, formaldehyde remains an indoor air quality issue. Due to its widespread diffusion it has been recognised as the most critical substance for indoor air quality (Kotzias et al, 2005).

Though formaldehyde is an indoor air pollutant that has been acknowledged and measured broadly for decades across Europe, and considering its large spreading

and the concern for human health, representative and accurate data describing indoor exposure to formaldehyde in Europe are still scarce.

Figure 1.2.1 Urea-formaldehyde resin



Occupational exposure to formaldehyde is principally due to thermal or chemical decomposition of formaldehyde-based resins, to the combustion of organic compounds, and emission from aqueous solutions (i.e. in laboratories and hospitals). Particularly, due to the volatile nature of formaldehyde, the latter is characterised by peaks of concentration that can range levels of several ppm if no containment measures (i.e. exhaust hood) are put in place (Orsiere et al, 2006).

1.3 Health effects

1.3.1 Human toxicity

Being a highly reactive chemical, formaldehyde causes tissue irritation and damage on contact. Due to its high volatility, the major and, most significant for human health, route of exposure is inhalation, either for indoor or occupational settings. Formaldehyde concentrations associated with adverse effects in humans show wide inter-individual differences. Predominant symptoms and signs of exposure by inhalation in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lacrimation, sneezing, coughing, nausea and

dyspnoea. Though oral exposure is rare, formaldehyde ingestion results in severe, corrosive, damage to the gastrointestinal tract, followed by CNS depression, myocardial depression, circulatory collapse, metabolic acidosis, and multiple organ failure (NTP 2010).

Controlled conditions studies on humans are relatively rare. On the opposite, community or work surveys are found very often in scientific literature. Generally, these papers do report the air levels of formaldehyde that were associated with health symptoms among people exposed.

Respiratory tract and eye irritation, and changes in odour threshold, have been reported in numerous surveys conducted among general population, even at concentration lower than 0.1 ppm. In occupational settings, reported effects include allergic contact dermatitis, histopathological abnormalities such as hyperplasia, squamous metaplasia, and mild dysplasia of the nasal mucosa, occupational asthma, reduced lung function, altered immune response, and hematotoxicity (IARC 2006). Some surveys conducted on workers in China suggest that long-term exposure to formaldehyde can cause leucopoenia. Particularly, one study reported that a significantly higher percentage of formaldehyde-exposed workers had blood cell abnormalities (leucopoenia, thrombocytopenia, and depressed serum haemoglobin levels) compared to unexposed controls (reviewed by Tang et al. 2009).

Higher rates of spontaneous abortion and low birth weights have been reported among women occupationally exposed to formaldehyde (IARC 2006, Saurel-Cubizolles et al. 1994).

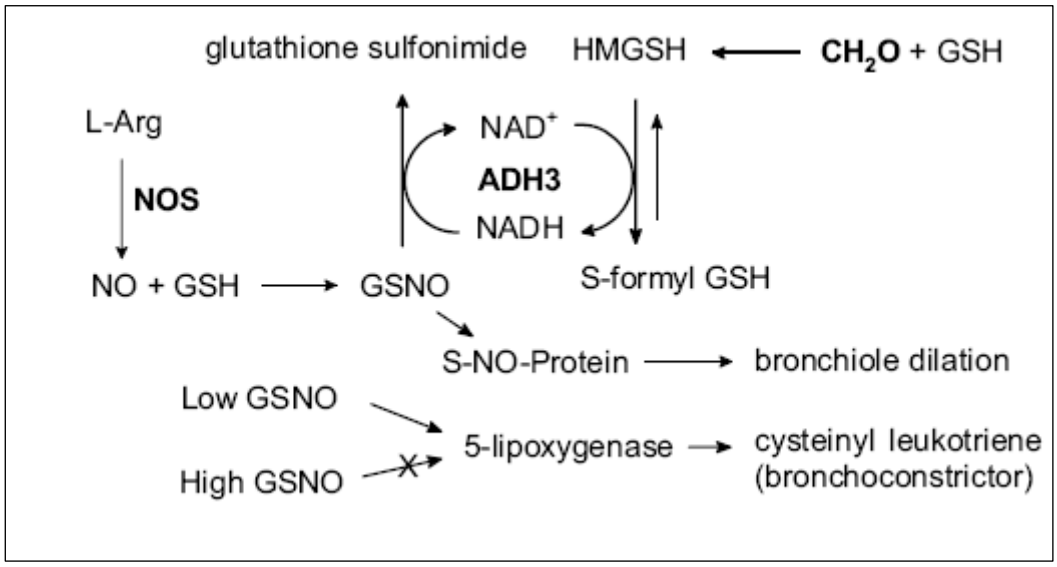
Recent literature data highlight the role of recurrent short-term peak exposures, rather than exposure to constant formaldehyde levels, in adversely affecting upper airways. One study in particular, monitored the health outcomes of a group of 21 volunteers exposed to several levels of formaldehyde in controlled conditions, with and without concentration peaks over a 10-week period, using a repeated exposure design (Lang et al., 2008). Eye irritation was found to be the most sensitive parameter. Eye and nasal irritation were objectively observed at continuous exposure to 0.5 ppm with peaks of 1 ppm exposure, but not at constant exposure to 0.5 ppm. Effects reversed 16 hours after the end of the exposures. No significant treatment effects of nasal flow and resistance, pulmonary disfunction, and reaction times were observed. It was concluded that a No Observed Effect Level (NOEL) for subjective

and objective eye irritation is 0.5 ppm in case of constant exposure levels, and 0.3 ppm with peaks of 0.6 ppm in case of short-term peak exposure.

Another study performed on asthmatic volunteers in controlled conditions was conducted in 2006 to evaluate the influence of pre-exposure to low-dose formaldehyde (100 µg/m^3, 0.08 ppm, for 30 min) on bronchial response to a mite allergen (Casset et al. 2006). Patients developed an immediate bronchial response at a significantly lower dose of mite allergen than after fresh air exposure, suggesting that formaldehyde might be involved in asthma exacerbation.

A possible mechanism to explain the association between formaldehyde exposure and asthma was proposed by Californian Office of Environmental Health Hazard Assessment (OEHHA, 2008). This complex metabolic pathway involves several enzymes and molecules as it is shown in Figure 1.3.1.1. In particular, it is hypothesised that formaldehyde plays a role in the dis-regulation of nitric oxide (NO), and this might help to explain the variety and variability in manifestations following formaldehyde inhalation. Further, is believed that genetic variation among individuals in the alcohol dehydrogenases affects individual responses to formaldehyde. It is concluded that although human studies investigating asthma, atopy or hyper-sensitisation due to formaldehyde exposure are not entirely consistent with each other (and there is a potential for confounding in each), taken together they suggest that children may be somehow more sensitive to formaldehyde than adults.

Figure 1.3.1.1 Formaldehyde-dehydrogenase (ADH3) mediated metabolism hypothesis (from OEHHA RELs, 2008).



1.3.2 Animal toxicity

The toxic effects of formaldehyde in experimental animals include irritation, cytotoxicity, and cell proliferation in the upper respiratory tract, ocular irritation, pulmonary hyperactivity, bronchoconstriction, gastrointestinal irritation, and skin sensitization. Other reported effects include oxidative stress, neurotoxicity, neurobehavioral effects, immunotoxicity, testicular toxicity, and decreased liver, thyroid gland, and testis weights (IARC 2006, Aslan et al. 2006, Sarsilmaz et al. 2007, Golalipour et al. 2008, Özen et al. 2005, Majumder and Kumar 1995).

Toxicological data from long-term studies seem to prove that irritant effects are concentration rather than dose (i.e, concentration x time) depended. Paustenbach 1997, OEHHA 2008 and others reviewed several chronic and sub-chronic studies on animals (Rush et al 1983, Wilmer et al 1989, Woutersen et al 1989), which suggest the concentration-dependent nature of irritation and cytotoxicity due to formaldehyde exposure. OEHHA deems that No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effects Levels (LOAELs) are similar in the reviewed studies regardless of exposure duration. Also pulmonary functionality was reported to be not affected in sub-chronic exposure to formaldehyde concentrations below 2 ppm.

Time-effect relationships of formaldehyde concentrations on airways was investigated in two studies (Nielsen et al. 1999, Andersen et al. 2008) particularly. In the first study (Nielsen et al. 1999), several respiratory parameters in relation to formaldehyde exposure were monitored and a NOEL value of 0.3 ppm was found in mice, comparing animal to human sensitivity to the substance .

In a more recent study (Andersen et al, 2008), endpoints considered included inflammatory infiltrate, epithelial hyperplasia and genomic signature in rats. Inflammatory response was observed starting from 0.7 ppm, while a trend toward altered gene expression was observed between 0.7 and 2 ppm. As regards cell proliferation no effect was found below 2 ppm.

In vitro studies have demonstrated that formaldehyde is directly cytotoxic and affects cell viability, cell differentiation and growth, cell proliferation, gene expression, membrane integrity, mucociliary action, apoptosis, and thiol and ion homeostasis (IARC 2006). Since metabolism of formaldehyde is glutathione-dependent, cells

depleted of glutathione are more susceptible to formaldehyde toxicity (Ku and Killings 1984).

1.3.3 Carcinogenicity

A large number of epidemiological studies evaluated the relationship between formaldehyde exposure and carcinogenicity in humans, revealing an association between exposure to formaldehyde and cancer in humans. Findings show increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia among individuals with higher exposure to formaldehyde (either exposure level or duration), which could not be explained by chance, bias, or confounding factors.

An increased risk for nasopharyngeal cancer was found among individuals with the highest formaldehyde exposure in numerous case-control studies (Vaughan et al. 1986, 2000, Roush et al. 1987, West et al. 1993, Hildesheim et al. 2001). Excess nasopharyngeal cancer mortality associated with formaldehyde exposure was observed in the US National Cancer Institute (NCI) cohort of industrial workers (Hauptmann et al. 2004). Further, positive exposure-response relationships were found both in a large multi-centre case-control study (Vaughan et al. 2000) and in the NCI cohort (Hauptmann et al. 2004).

Concerning sinonasal cancer, an increased risk was found in population-based case-control studies (Olsen et al. 1984, Olsen and Asnaes 1986, Hayes et al. 1986, Roush et al. 1987, Luce et al. 1993). A pooled analysis of 12 case-control studies (Luce et al. 2002) found also an excess of sinonasal cancer. In most studies, estimates of increased risk for both sinonasal adenocarcinoma and squamous-cell carcinoma; were statistically significant for individuals ever exposed to formaldehyde, or with higher probability or higher levels of exposure.

An association between excess mortality from leukemia or combined lymphohematopoietic cancers has been reported in several cohort studies, including studies of professional groups (especially embalmers) and some of the studies of industrial cohorts (NTP 2010). Some of these studies reported positive exposure-response relationships for combined lymphohematopoietic cancer or specific subtypes (Beane Freeman et al. 2009, Hauptmann et al. 2009). In particular, the strongest associations were observed for myeloid leukemia. The most informative studies for evaluation of the risk of this cancer are the large cohort studies (NCI,

NIOSH, British cohorts) of industrial workers and the NCI nested case-control study of lymphohematopoietic cancer in embalmers. Three of these (NCI, NIOSH and embalmers), found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships (Beane Freeman et al. 2009, Pinkerton et al. 2004, Hauptmann et al. 2009). In contrast, no association between these types of cancer was found among British chemical workers cohort (Coggon et al, 2003). Exposure to peak levels of formaldehyde (of 4 ppm and above) was associated with increased mortality of lymphohematopoietic cancers among workers in the NCI cohort study (Beane Freeman et al. 2009), while no associations were found with cumulative or average exposure. In the smaller industrial cohort studies, some reported excesses for all lymphohematopoietic cancers combined among formaldehyde-exposed workers (Bertazzi et al. 1989, Stellman et al. 1998) or leukemia (Hansen and Olsen 1995, 1996), but others observed no association for all lymphohematopoietic cancers combined (Andjelkovich et al. 1995, Stern 2003, Pinkerton et al. 2004) or leukemia (Andjelkovich et al. 1995, Stellman et al. 1998, Stern 2003). With respect to other case-control studies, a population-based study found no clear association between leukemia and exposure to formaldehyde (Blair et al. 2001), and two nested case-control studies reported statistically non-significant increases in leukemia risk based on small numbers of exposed cases (Partanen et al. 1993, Ott et al. 1989).

Formaldehyde has been tested for carcinogenicity in mice, rats, and hamsters. Studies reviewed include chronic and sub-chronic inhalation studies in mice, rats, and hamsters; chronic and subchronic drinking-water studies in rats; and one chronic skin-application study in mice (NTP. 2010).

Long-term exposure inhalation to formaldehyde by inhalation caused nasal tumours, both benign (polypoid adenoma) and malignant (predominantly squamous-cell carcinoma but also adenocarcinoma and carcinoma) in male and female F344 rats (Kerns et al. 1983, Monticello et al. 1996, Kamata et al. 1997), male Sprague-Dawley rats (Sellakumar et al. 1985), and male B6C3F1 mice (Kerns et al. 1983a). In particular, long-term exposure to 6 ppm formaldehyde and above caused squamous cell carcinomas of the nasal cavity of rats with a non-linear, biphasic concentration-

response relationship having the breakpoint at or above 2 ppm. (Kerns et al 1983, Monticello et al. 1996).

Nasal tumours were observed after 13 weeks exposure in male Wistar rats also (Feron et al. 1988). Although the increased incidences of nasal tumours in mice and in the short term exposure study in rats were not statistically significant, they were considered to be biologically significant because of the rarity of this type of tumour.

One of the most accredited hypotheses to date explaining carcinogenic pathway has been based primarily upon data derived from laboratory studies. Increased cellular proliferation, as a consequence of epithelial cell toxicity, appears to be the most significant determinant of tumour progression associated with formaldehyde inhalation. Formaldehyde concentration, rather than duration of exposure, seems to be related to histopathological effects and increased proliferation of epithelial respiratory cell in the nasal cavity. Further, the extent of proliferative response depends on the specific site of the nasal cavity being examined (Liteplo and Meek, 2003). These regions are similar to those where tumours are observed. Significant increases in endpoint considered such as cytotoxicity, increased epithelial cell proliferation, and even DNA-cross linking, though non-linear, are observed at concentration of 4 ppm (Casanova & Heck, 1987). This might be correlated with the concentration at which mucociliary clearance is inhibited (> 2 ppm ca.) and gluthatione-mediated metabolism saturated (4 ppm) (Morgan et al, 1986a, Casanova et al, 1994).

Several studies consider formaldehyde exposure associated with multiple modes of action related to carcinogenicity, such as DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects (binding to lysine residues of histones), glutathione depletion, oxidative stress, and cytotoxicity-induced cellular proliferation (Lu et al. 2008, Guyton et al. 2009, NTP 2010). Although an evidence for a genotoxic mode of action for formaldehyde-induced cancer seems possible, the mechanisms by which formaldehyde causes cancer are not completely understood.

1.4 Classification

Formaldehyde classification, especially concerning carcinogenicity, presents relevant discrepancies among different countries.

1.4.1 European Union

In EU, accordingly to Directive EEC/67/548, it is classified as Carcinogen Category 3. This group includes *"substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2".* This means that 'there is a limited evidence of carcinogenic effect'. Further, is classified as Toxic (T) and Corrosive (C), and the following Risk and Safety Phrases are given:

- R23/24/25 : Toxic by inhalation, in contact with skin and if swallowed.
- R34 : Causes burns.
- R40 : Limited evidence of a carcinogenic effect.
- R43 : May cause sensitization by skin contact.
- S1/2 : Keep locked up and out of the reach of children.
- S26 : In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
- S36/37/39 : Wear suitable protective clothing, gloves and eye/face protection.
- S45 : In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
- S51 : Use only in well-ventilated areas.

Regarding chemical safety, due to its low flash point, it is classified as a flammable gas.

Classification of its commercialised products depends on concentration range. In table 1.4.1 specific concentration limits are reported.

Table 1.4.1.1 Concentration limits for formaldehyde classification (67/548/CEE)

Concentration ranges	Classification
C ≥25 %	T, C; R23/24/25-34-40-43
5 % ≤ C < 25 %	Xn; R20/21/22-36/37/38-40-43
1 % ≤ C < 5 %	Xn; R40-43
0,2 % ≤ C < 1 %	Xi; R43

New CLP Regulation (Reg. (EC) No. 1272/2008 on Classification, Labelling and Packaging) does not produce substantial differences in classification from Dir. EEC/67/548. Concerning carcinogenicity, formaldehyde is listed in Group 2 ("*suspected human carcinogen*").

Already in 2005, France proposed to classify formaldehyde as Category 1 carcinogen, with the phrase R49 "*can cause cancer if inhaled*". In spite of this, the European Chemicals Bureau, did not reach a decision to change the classification at that time. Recently this year (September 2010), French government advanced a reclassification proposal, supported by a dossier submitted to the European Chemicals Agency (ECHA), requesting its upgrading among Category 1 carcinogens. According to ECHA, the dossier is currently being processed. If the accordance check is fulfilled and it is accepted by the Member State Committee (MSC) for consideration, a public consultation could start by the end of the year or early 2011. A category 1 or 2 classification under the Dir. EEC/67/548, or a 1A or 1B classification under CLP, would have significant implications for use of formaldehyde. In fact, as a consequence of a potential reclassification, also formaldehyde inclusion in REACH Annex XV (list of substances subject to authorisation), is to be considered a likely outcome.

As regards other aspects of REACH Regulation it is not considered "*Persistent Bioaccumulating Toxic (PBT*)" or "*very Persistent very Bioaccumulating (vPvB)"* substance, while being a High Production Volume Chemical (HPVC) its deadline for REACH registration is 30th November 2010 (its dossier has already been submitted).

Formaldehyde is not listed in the Annex I of Regulation (EC) No 689/2008 (export and import of dangerous chemicals regulation), nor on a priority list for risk assessment. However, formaldehyde is banned from use in certain applications (preservatives for liquid-cooling and processing systems, slimicides, metalworking-fluid preservatives, and antifouling products) under the Biocidal Products Directive (Directive 98/8/EC).

1.4.2 IARC and US classification

In 2004, based on observed excess risk of nasopharyngeal cancers in the considered cohorts, the International Agency for Cancer Research (IARC) reclassified formaldehyde as carcinogen to humans in Group 1 (Cogliano, 2005, IARC 2006). In October 2009, IARC concluded on the basis of the outcomes from cohort studies, that there is sufficient evidence for a causal association between formaldehyde and leukemia.

Outside EU, other re-considerations of formaldehyde classification regarding carcinogenicity have taken place in last year. In particular, in United Stated, on January 2010 the Department of Health and Human Service re-classified formaldehyde from "*reasonably anticipated to be a human carcinogen*" to '*known human carcinogen'* through its National Toxicology Program (NTP).
In addition, last June, the US Environmental Protection Agency (US EPA) released for public consultation a draft report wherein it is affirmed that sufficient epidemiological evidence to consider formaldehyde '*carcinogenic to humans by the inhalation route of exposure'* both exists for naso-pharyngeal and lympho-hematopoietic cancers. Public consultation was expected to be closed within 3 months (September 2010), nevertheless, no news has been posted on EPA website to date (November 2010). Currently, official EPA classification regarding carcinogenicity is B1, "*probable carcinogen*".

1.5 Project objectives

The project has been developed around two major purposes.

The first one has been to perform a hazard characterisation of formaldehyde in order to calculate health-based reference exposure limits for concentrations in indoor air. This study has been carried out participating at European Project "*INDEX UPRIC 2009*" funded by DG SANCO.

The first edition of the project INDEX "*Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU*", funded by DG SANCO in 2004, aimed to perform risk assessments for several pollutants typical of indoor environments and the proposal of reference limit of exposure and/or risk management measures (Kotzias et al, 2005). Outcomes have contributed to the development of strategies at EU level for indoor air quality management. In 2009, DG SANCO re-funded an update of the project, with particular regards to formaldehyde. INDEX-UPRIC (UPdate of PRIority compounds) aimed to review recent scientific data in order to re-consider reference values proposed in 2005. From selected results of scientific literature and an innovative approach in uncertainty factors application, new reference limits have been calculated for formaldehyde in indoor settings and proposed at EU level.

The second objective of the project has based its rationale from the outcomes of INDEX project. From the hazard characterisation of formaldehyde, it seems that recurrent, short-term, peak exposures**,** rather than exposure to constant levels, are expected to adversely affect eyes and upper airways in exposed subjects. Secondly, exposure to formaldehyde in occupational settings, and particularly in Pathology labs, seems to be characterised by marked fluctuations and peaks of concentration. To perform a correct exposure assessment in Pathology Units, and to eventually associate exposure levels with health effects, an in-depth understanding of exposure is a requirement. The project aimed to reach this goal through the development of detailed Exposure Scenarios and the comprehension of concentration fluctuations during specific tasks in Pathology Units of two different hospitals.

Materials and Methods

2.1 European Project INDEX-UPRIC 2009

2.1.1 Literature review

An extensive literature review of the period 2004-2009 about crucial topics regarding formaldehyde has been carried out. Also relevant previous studies and reviews were reconsidered. Data have been searched for formaldehyde exposure (especially on community surveys) and health effects by inhalation (both on volunteers and animals). Epidemiological data concerning carcinogenicity have been taken into account as well. A particular attention has been paid to reports published by national or international institutions. Due to their use for risk assessment and for exposure limits calculation by several institutions, surveys at the workplace have been carefully evaluated.

Web search of scientific papers about formaldehyde health outcomes and cohort studies has been based mostly on digital archives PubMed and Web of Science. Key words of the search have been "formaldehyde toxicology", "formaldehyde irritation", "formaldehyde effects", "formaldehyde asthma" and "formaldehyde cohort". To seek for exposure levels among population both above-mentioned archives and Google have been used. Key words have been "formaldehyde surveys", "formaldehyde exposure", "and formaldehyde indoor". Web sites of major national and international organisations have been consulted looking for reports, evaluations, if present, the classification proposed and any other relevant news or communication on formaldehyde. Workplace surveys have been initially identified from the bibliography of organisation reports; further the search has deepened following usual scientific

archives cited above with key words “formaldehyde work exposure” and “formaldehyde monitoring”. Also a number of in-silico studies have been considered, since when their significance appeared from the literature review.

Following the search, relevant literature has been catalogued. International organisation guidelines together with scientific reviews and risk evaluations have been separately summarised by:

- health outcome:
    - toxicological effect except cancer and
    - carcinogenicity;
- setting:
    - indoor (home, kindergarten or office) or
    - occupational.

Relevant scientific papers such as human, animal and in-silico studies have been arranged by condition (controlled or uncontrolled exposure) and by outcomes:

- health effect on humans, excluding carcinogenicity:
    - subjective discomfort,
    - signs of irritation of eyes and upper airways,
    - pulmonary function,
    - occurrence of asthma or hypersensitivity (hyperreactive airways?),
    - genotoxicity;
    - histopathological changes;

- health effect on animals, excluding carcinogenicity:
    - histopathological/biochemical changes in nasal tissues,
    - pulmonary function,
    - genomic signature;

- In-silico studies.

2.1.2 Calculation of reference exposure values

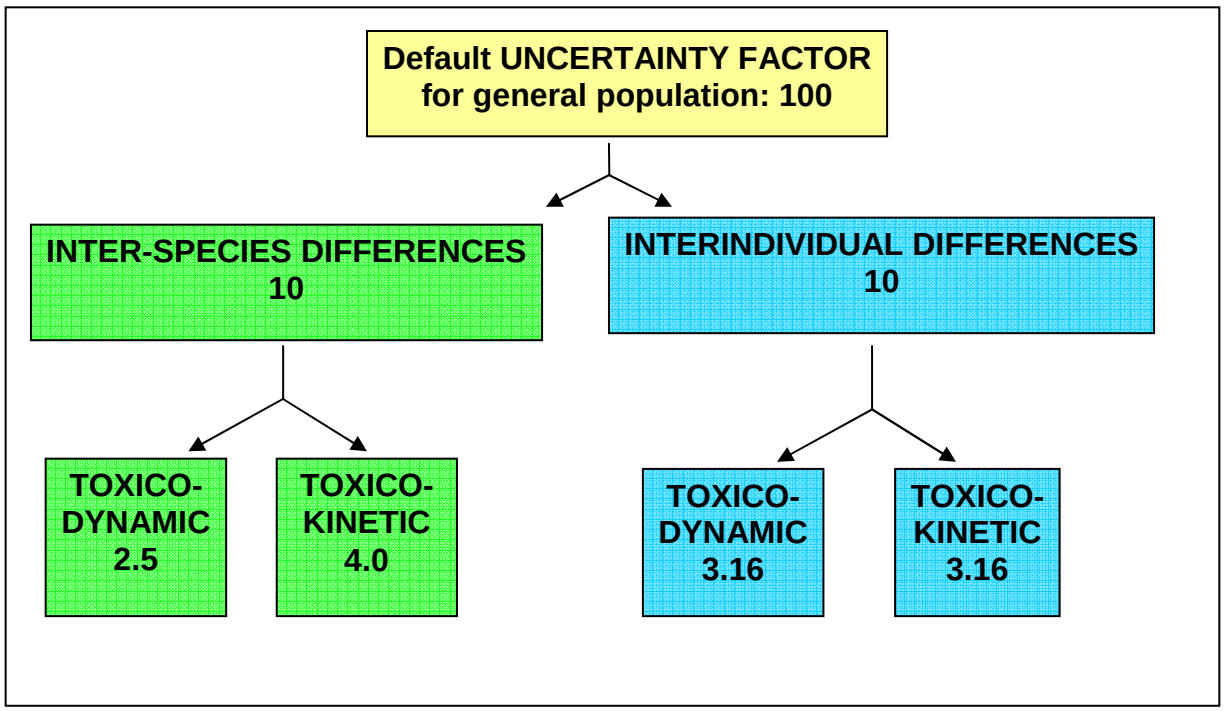
The derivation of reference exposure values has been based on recent human and animal studies. The choice of pivotal studies has been based on the following parameters.

First, the study must have been conducted under well defined and controlled conditions, especially with respect to air concentrations of formaldehyde and length of exposure (via inhalation. Second, health outcomes investigated have to be unequivocally attributed to formaldehyde exposure, to be extensively documented, and to occur at low levels of exposure (most sensitive endpoint).

The endpoint chosen was irritation of eyes (in humans) or upper airways, especially nose tissues (in animals). Eye irritation in humans has been measured with two parameters, conjunctival redness and eye blinking frequency (Lang et al, 2008). Irritation of upper airways is deemed to be due to sensory irritation caused by the direct stimulation of the trigeminal nerve endings of the upper respiratory tract. This effect is measured as the decreases in respiratory rate in mice (Nielsen et al, 1999). In rats irritation signs have been identified as inflammatory infiltrates development at various nasal tissues (Andersen et al, 2008).

Based on these criteria, two animal (on mice and rats) and one human study have been chosen for formaldehyde hazard assessment (characterisation)
To calculate reference exposure values, chemical-specific *uncertainty factors* (also known as assessment factors) have been applied as described in a document published by World Health Organization International Programme on Chemical Safety (IPCS, 2006) to toxicological endpoint values such as NOAELs or LOAELs. This report present several indications for the use of adjustment or uncertainty factors in the calculation of health-base exposure limits for chemical substances. It distinguishes and assigns different weights to toxicokinetic and toxicodynamic components. As depicted in figure 2.1.3.1, the default uncertainty factor used to set exposure limits for general population accounts for both inter-species (factor of 10) and inter-individual differences (factor of 10) evenly. Here specific weights are given for the toxicodynamic and toxicokinetic components, accounting for inter-species or inter-individual variability.

Figure 2.1.2.1 Different weights for toxicokinetic and toxicodynamic components from WHO, Harmonisation Project Document No. 2, 2005.



Further, warnings are given on the nature of chemical. Particularly, a Chemical Specific Assessment Factor (CSAF) should be applied, and has to be determined by the chemical-specific data. It is reported that "*an inter-species factor could be less than 1 if humans had lower target tissue exposure to the active chemical moiety for the same external dose or showed lower tissue sensitivity*".

2.2 Exposure characterisation and scenarios in hospitals

2.2.1 Identification of uses and exposure determinants

Exposure characterisation of formaldehyde in a Pathology Unit has started from the building of Exposure Scenarios. An Exposure Scenario is "*a set of information describing the conditions under which the risks associated with the identified use(s) of a substance can be controlled. It includes operational conditions (for example the duration and frequency of use or the amount used, the process temperature or the pH) and necessary risk management measures (e.g. local exhaust ventilation or a certain type of glove, waste water and waste gas treatment)*". It is an iterative process which is part of the Chemical Safety Assessment (CSA) under REACH Regulation. In particular, the preparation of Exposure Scenarios is mandatory for the registration when a substance is manufactured or imported in quantities of 10 tonnes per year and above and classified as dangerous or as PBT (Persistent Bioaccumulative Toxic) or vPvB (very Persistent very Bioaccumulative). Relevant exposure scenarios will be annexed to the Safety Data Sheets that will be supplied to downstream users and distributors.

This part of the work has been based on REACH Regulation Technical Guidance, particularly on the document *"Guidance on information requirements and chemical safety assessment - Part D: Exposure Scenario Building"* (ECHA, 2008).

The two hospitals chosen for the purpose are located on the territory of the municipality of Milan. Pathology Units presents differences in size, number of operators occupied, instruments and organisation adopted. Nevertheless, the same checklist (based on REACH technical guidance) has been applied during interviews with personnel (pathologists, students, technicians and other attendants).

At first, uses of formalin within the unit have been identified: all direct tasks, which involve the handling of formalin (i.e. inclusion of specimens in formalin, dilution, disposal, etc) and indirect, which do not bring the operator to the direct handling of formalin (i.e. colouration, inclusion in paraffin, etc) have been recognised from dilution, to its disposal. For each one of them a description of the activity is given and, when possible, of exposure determinants such as concentration, frequency, quantity, duration, existent mitigation measures (i.e. ventilation, extracting devices or chemical hood) and observations noted during the first inspection. Further, each room

interested by the use of formalin has been numbered. The checklist headlines are reported in table 2.2.1.1.

Based on the exposure determinants and conditions of use, it has been possible to identify some uses as *critical* for operator exposure. Particular attention has been paid to those tasks in which there is a direct use of formalin. In fact, the monitoring survey has been planned to measure air concentrations during selected, critical tasks, where possible one by one, trying to avoid overlapping. In such a way, air levels of formaldehyde and their fluctuations can be better understood and associated to single tasks.

Table 2.2.1.1 Checklist for identification of formalin uses and other exposure determinants in Pathology Units.

Task	Description	Environment	Concentration	Quantity	Frequency	Duration	Existing mitigation measures	Observation during inspection	Air monitoring: necessary?	Air monitoring technique chosen
Task 1	Brief description of the operation	Room No #	% v/v or m/v of active substance	Volume used (if not possible give an approximate estimation)	Say if the task is performed daily/ # times per week.	Seconds/minutes/ hours.	Ventilation or exhaust extraction (aspirated bench, chemical hood)	Report any peculiarity.	Yes/No	Passive/Active/In-continuous/all of them

2.2.2 Air monitoring techniques

The air sampling techniques measuring formaldehyde are crucial to perform an Exposure Characterisation. To date, traditional air monitoring for the measurement of formaldehyde levels, have been mostly conducted using both active and passive devices. Those methods can provide air concentrations as Time Weighted Average (TWA), over 15-20 minutes with active devices and over hours to days when using passive techniques. Thus, traditional air monitoring may not be able to identify short-term concentration fluctuations typical of pathology labs. In-continuous gas sampler could present an effective method to depict formaldehyde fluctuations and peaks in laboratories. To conduct a detailed monitoring and to assess the suitability of different sampling methods, a simultaneous air monitoring utilising three techniques has been planned.

Since the beginning of the project, the use of a sampling method capable to depict the extent of concentration peaks and exposure variability has been taken into account. To do this, a brief literature search has been carried out, and some companies have been consulted. Three detection techniques have been carefully considered: Photo-acoustic gas monitor, infrared sampler, electro-chemical cells. The latter has been considered at first, but it has been discounted due to the difficulties in device calibration. Bruel Kjaer 1302 photo-acoustic gas monitor (following Photo-acoustic) has then been chosen. It presents several remarkable characteristics. It is a quantitative gas analyser, controlled by a microprocessor, and it works as in-continuous detector for several gases (depending on the filters chosen). It gives real time concentrations within 120 seconds or less, thus it is very likeable to detect peak levels. The measurement is based on the principle of photo-acoustic/infra-red detection method, in particular on the capability of the molecules to absorb energy as infra-red light and release it in the form of heat (with vibrational motions). An air sample is drawn and sealed into an analysis cell inside the instrument. The light produced passes through an optic filter, which selects the proper wave length to be transmitted to the cell. One single wave length is thus transmitted at a given instant. When the light emitted is absorbed, selectively, by the gas, its temperature rises. As the light is pulsing, gas temperature rises and decreases causing a pressure variation. Therefore, an acoustic signal proportional to the gas concentration is produced. Two microphones are present inside the cell to detect the signal. When a certain gas measuring is done, a rotation of the whirl on which filters are fixed occurs

and a new measure can start. It takes about 2 minutes to measure 5 different gases and aqueous vapour in the same air sample. Further, Photo-acoustic is calibrated to compensate some potential interferences between different compounds (i.e. formaldehyde and methanol). Output data (air concentrations) are immediately visualised on the display. Data can also be memorised, send to a printer, or transferred into a text file ASCII (to be imported in a spreadsheet for elaboration). The range of concentrations that can be measured is very wide, from 0.04 to 10 ppm (calibrating range).

Figure 2.2.2.1 In-continuous gas sampler: Bruel Kjaer Photo-acoustic monitor 1302

Many methods either active or passive have been evaluated to understand their suitability to the project objectives. Well known methods such Radiello® for passive and DinitroPhenylHydrazine (LpDNPH) cartridges for active monitoring have been initially considered, then discarded because alternative, more fit-to-purpose techniques have been identified.

Dräger Bio-check F, colorimetric disposable samplers have been chosen for passive air sampling. This method gives a two-hours TWA, meaning that the measure of

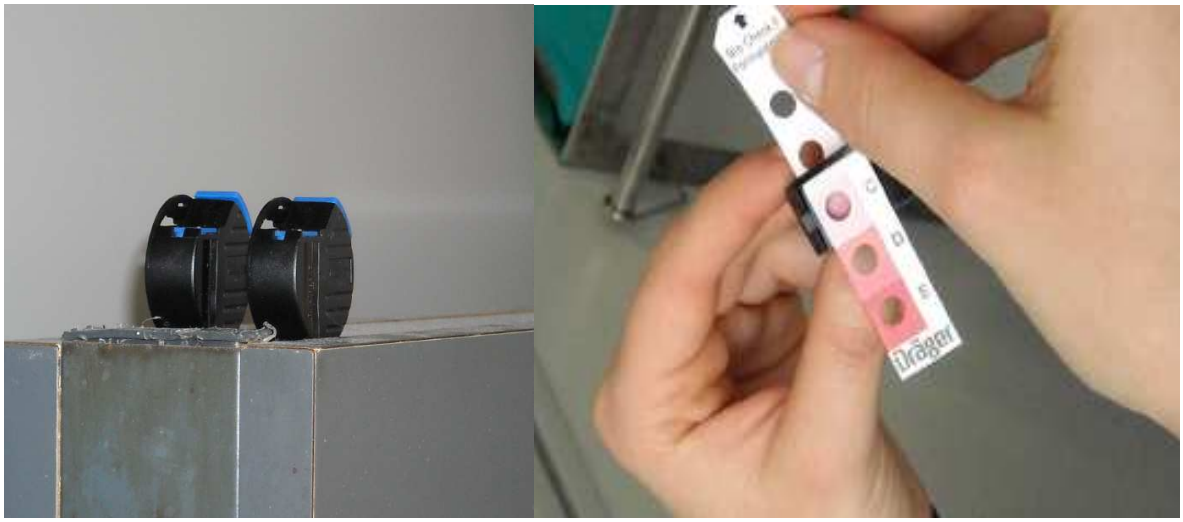
formaldehyde takes two hours once the device is activated. The principle of this simple sampler is an enzymatic reaction, which produces a coloration of the substrate in presence of formaldehyde. In this way the reading is semi-quantitative according to concentration ranges as reported in table 2.2.2.1.

Table 2.2.2.1 Dräger Bio-check F concentration ranges in ppm*

A	B	C	D	E
≤ 0.05	0.05 - 0.1	0.1 - 0.2	0.2 - 0.3	≥ 0.3**

*Part per million; 1 ppm = 1.24 mg/m^3 (20℃; 1atm)
**TLV (US ACGIH)

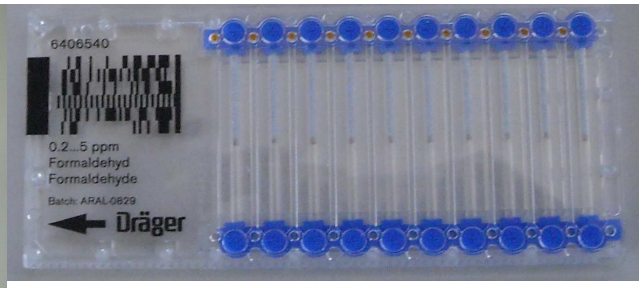
Figures 2.2.2.2a and b. Passive sampler Dräger Bio-check F



Among active methods, Dräger CMS (Chip Measurement System) has been chosen for its easiness to be transported and moved while monitoring, and for its capability to give an immediate response (no need of lab analysis). It is a robust air sampling device based on photochemical spectrometry. It composed by three main parts:
-pump for active sampling;
-chip, containing 10 micro-vials. Each micro-vial contains micro-granules which will be soaked by the chemical reagent;
-analyser.
When a connection has been established between incoming gas and conduction system a micro-vial is open and the gas is pushed inside by a special inside pump.

The range of concentration measured, even if not so wide, is typical of levels detected in laboratories (0.2 to 5 ppm). Measuring time varies from about 4 to 12 minutes depending on the concentration (short-term measurements). Being not possible to fix automatically an interval of measurement, a constant surveillance and a manual activation are needed.

Figures 2.2.2.3a and b. Active sampler Dräger CMS and chip containing 10 micro-vials.



2.2.3 Monitoring campaigns setting

Preliminary screening

A preliminary monitoring survey has been conducted at University Hospital Luigi Sacco. This survey had the purpose to inspect the labs, to interview the personnel and identify tasks and exposure determinants. It included also a preparatory screening of formaldehyde concentration by ambient and personal sampling. Dräger Bio-check F passive sampler has been used to detect two-hours TWA in three rooms: dissection room, central laboratory (where various operations occur) and the archive located in the basement.

Exposure modeling exercise

Before starting with monitoring campaigns, exposure estimation has been carried out utilising the software ConsExpo 4.1 (see description in Appendix A). Input data inserted try to simulate a plausible routine task which could be pouring a certain amount of formalin from a container in dissection room. Results of the exposure estimation have been then compared with level of formaldehyde measured in laboratories, in particular with those found in dissection room of University Hospital L. Sacco. Input data and outcomes of the exercise have been reported in Appendix A.

Testing of the three techniques

Before starting the paired monitoring with the three techniques, an experiment has been conducted in order to test the three instruments during the same situation. The test consisted in measuring environmental levels of formaldehyde following formalin pouring into an exposure room. It has been conducted in a laboratory provided with two chemical extraction hoods. The first one has been sealed with plastic paper and kept switched off to work as exposure room; the other one has been switched on in order to ensure safe conditions in the lab. Environmental conditions, i.e. ventilation and temperature, have been kept under control until the test ended.

A known amount of formalin (4% m/v formaldehyde) has been poured on filter paper in a container under an extraction hood used as exposure room. Another chemical extraction hood was switched on in order to ensure safe conditions in the lab.

Photo-acoustic, CMS and Bio-check F samplers have been placed inside the exposure room and started monitoring air concentrations. Formaldehyde levels were

expected to follow the dilution model described in the formula below (Clausen et al, 1993).

$$C_t = A \cdot M_0 \cdot k_1 \cdot \frac{\left(e^{-k_2 t} - e^{-k_1 t} \right)}{V (k_1 - k_2)}$$

Where:

A: (area of emitting surface) [m^2]

M_0: (initial mass) [mg];

k_1= emission rate [m^2/m^3];

k_2: air exchange rate [1/t];

V: room volume [m^3].

Data detected by photo-acoustic method fit a decay model (see Appendix B). As expected CMS and Bio-check F samplers, gave TWA results, and were in good accordance with photo-acoustic measurements.

During this test a problem with CMS sampler has come out. Some chips were not able to read the 'blank', namely concentration below detection limit (0.2 ppm). In a "control" room, where exposure to formaldehyde levels are expected to be exceedingly low, values higher than 0.2 ppm have been measured, a sort of "false positive". The supplier consulted deemed that it must have been a single chip rather than a whole apparatus problem.

Thus, to guarantee a sound use of the instrument and reliable results a method for chip selection has been set up. Prior to be used for monitoring purposes, at least blank reading for 2 vials each chip (on 10 vials) is required. Chips which gave one false positive have been discarded.

Monitoring surveys

Two monitoring surveys have been planned in the two hospitals. Taking into account exposure determinants, tasks identified as critical have been selected for the monitoring with the three techniques. Other tasks or situation not expected to present high exposure levels have generally been monitored with passive sampler Bio-check F only. The careful surveillance of the operation during the measurement has permitted to notice and record any peculiar circumstance as well as potential

misuses, or even accidental situation (i.e. pouring formalin on the floor or on the bench). Concentrations detected have then been compared to the Threshold Limit Value (TLV) for occupational exposure to formaldehyde adopted by the American Conference of Industrial Hygienists (ACGIH). A detailed Exposure Scenario for each use identified as critical, namely those tasks where concentrations clearly exceeded TLV-C (or at least for some of them taken together), has been built up and Risk Management Measures (RMMs) addressed specifically.

2.2.4 Data elaboration

Principle Component Analysis (PCA) has been used as an exercise on data obtained from the survey carried out at the University Hospital L. Sacco. Data from the monitoring at National Cancer Institute had a surplus of non-parallel measurements, rendering this type of analysis unreliable because of the poor level of variability of the data. The statistical unit used in the PCA data matrix has been the timing of measurement (sampling) by the three techniques. Only time units having all three measures have been analysed.

The aim of the PCA has been twofold: (a) to investigate the correlation among the outputs given by the three sampling methods and, (b) to see the profiles obtained for the three sampling techniques per task type. Bio-check F classes have been assigned as quantitative values, choosing representative values of 0.075 ppm for class B, 0.25 ppm for class D and 0.3 ppm for class E.

Data obtained with CMS and Bio-check F methods have been paired to each measurement obtained with Photo-acoustic. The PCA has then been applied to the matrix of the differences between measures and the ACGIH TLV set for formaldehyde. The graphical display chosen has been the *biplot*, in which the x and y axes are a linear combination of the three measurements and the vectors reflect the behaviour of the original values in the new orthogonal axes. The origin represents the TLV. Each point is a bi-dimensional representation of one moment in time, when measurements have been taken while a certain task was performed. Each task has been given a number that was used to label the points and this allowed comparisons of measurements according to task by projecting the single point onto the vectors. In fact, when the barycentre of each group of tasks is projected onto the vectors, the average profile of the task is obtained. Charts and outcomes are reported and discussed in Appendix C. The software used for the analysis has been XLSTAT Version 2010.5.08 - Copyright Addinsoft 1995-2010.

Results

3.1 European Project INDEX-UPRIC 2009

3.1.1 Levels of exposure among general population

Results of the indoor air formaldehyde measurements in 21 studies representing mostly Europe but including also North America, Australia and Japan are summarised in Table 3.1.1.1.

Between 2003 and 2005 the French Observatory on indoor air quality (OQAI) carried out a large monitoring survey in 567 dwellings randomly selected (Kirchner et al, 2006). Formaldehyde median indoor concentration, 95th percentile and maximum value of 7-day passive sampling in the bedroom (n=554) were respectively 19.6, 46.7 and 86.3 µg/m^3 (15.8, 37.7 and 69.6 ppb respectively). Still in France, aldehyde concentrations were measured through active sampling (duration of measuring varied from 30 to 95 min) in 162 homes in the Strasbourg area, in the frame of a case-control study pairing asthmatic and non-asthmatic people (Marchand et al, 2008). Measured formaldehyde mean indoor concentration was 32.2 ± 14.6 µg/m^3 (26 ± 11.8 ppb).

In Germany, children's bedrooms in 555 dwellings located in 150 cities were monitored by passive sampling during one week, between May 2003 and May 2006 (KUS, 2008). The geometric mean, the 95th percentile and the maximum value of formaldehyde indoor concentration, (n=586) were respectively 23.3, 47.7 and 68.9 µg/m^3 (18.8, 38.5 and 55.6 ppb). These levels were lower than the respective concentrations measured in the past years in the frame of the German Environmental Survey (GerES I 1985/86).

In Belgium, a measuring survey was carried out in 50 dwellings in the frame of the FLIES project (Flanders Indoor Exposure Survey) in January and February 2006 (VITO, 2007). Indoor formaldehyde mean concentrations in bedrooms and living rooms were 35, 37 and 21 µg/m^3 (28.2, 29.8 and 16.9 ppb) in urban areas, hot spots and rural areas respectively.

Much less information is available for formaldehyde levels in offices compared to residential settings. A large monitoring survey in offices was carried out in Germany between 2001 and 2004 in 419 rooms: a median indoor concentration of 28 µg/m^3 (22.6 ppb) was measured (BGIA, 2004). Over the period 2004-2007, the Joint Research Centre of the EC carried out the monitoring of priority pollutants for indoor air quality, including formaldehyde within the frame of the Indoor Air Monitoring and Exposure Assessment Project (AIRMEX) (Kotzias et al, 2009). The survey included monitoring in European public buildings and environments where children frequently stay, like schools and kindergartens. Formaldehyde concentrations in offices of public buildings (n=94) ranged from 3 to 33 µg/m^3 (from 2.4 to 26.6 ppb).

Measurements of formaldehyde indoor levels in schools and kindergartens in many European countries are available. In France, in the frame of the study ISAAC (International Study on Asthma and Allergies in Childhood), formaldehyde was measured in 401 classrooms of 108 schools located in six cities in 1999 (Strasbourg, Creteil, Reims, Marseille, Bordeaux, Clermont-Ferrand) (Annesi-Maesano et al, 2001). Concentrations ranged from 4 to 100 µg/m^3 (from 3.2 to 80.6 ppb) with a mean value of 27 µg/m^3 (21.8 ppb). In 50 Parisian kindergartens studied between 1999 and 2001, both in winter and summer seasons (n=222), indoor formaldehyde concentrations ranged from 1.5 to 56 µg/m^3 (from 1.2 to 45.2 ppb) with a median value equal to 14 µg/m^3 (11.3 ppb) (Domsic and Squinazi, 2001). In Strasbourg, formaldehyde concentrations have been measured through passive sampling during 48h in 111 schools (n=384 classrooms) and 33 day-care centres (n=142 rooms) between November 2004 and January 2005 (ASPA, 2005). Mean indoor formaldehyde concentrations were respectively 27 µg/m^3 (21.8 ppb) in primary schools, 22 µg/m^3 (17.8 ppb) in elementary schools, and 18 µg/m^3 (14.5 ppb) in day-care centres. Similarly, in the Rhône-Alpes region, formaldehyde concentrations have

been measured by passive samplers during 4,5 days in 28 schools and 22 day-care centres (n=150 rooms) between June 2006 and March 2007 (Rhône-Alpes, 2007). Mean indoor formaldehyde concentration was higher in schools than in day-care centres 24.1µg/m^3 (19.4 ppb) *versus* 18.6 µg/m^3 (15 ppb).

In Germany, in the region of South Bavaria the indoor air quality was evaluated in 92 classrooms in winter 2004-2005 and in 75 classrooms in summer 2005. Indoor formaldehyde concentrations ranged from 3.1 to 46.1 µg/m^3 (from 2.5 to 37.2 ppb) (Fromme et al, 2008).

In Belgium, Hainaut Province Sanitary Surveillance Centre carried out measurements in 25 day-care centres (passive sampling during 48 hours) between March and June 2008 (HVS, 2009). In one of them, formaldehyde concentration was above the 100 µg/m^3 (80.6 ppb) intervention value established by the Flemish Community; in 16 of them, the formaldehyde concentration was above the 10 µg/m^3 (8.1 ppb) objective value fixed by the authorities.

In nine Austrian schools, located both in urban and rural areas, a median of 30 µg/m^3 (24.2 ppb) and a maximum value of 136 µg/m^3 (110 ppb) have been reported for indoor formaldehyde concentration when sampling (active) one week long (LUKI, 2008).

Within the frame of the AIRMEX project (Kotzias et al, 2009), formaldehyde concentrations were measured in European kindergartens located in 11 European cities (n=57; 7 days passive sampling) between 2004 and 2007. The average concentration of formaldehyde was 17.4 µg/m^3 (14 ppb) and ranged from 1.5 µg/m^3 (1.2 ppb) to 49.7 µg/m^3 (40 ppb).

In the frame of BUMA project (Prioritization of Building Materials Emissions), monitoring surveys were conducted in two Mediterranean cities (Nicosia and Athens) in winter period, in four buildings in each city (one public building, one school and two houses) (Bartzis et al, 2009). Indoor formaldehyde concentrations ranged between 5.8 – 43.2 µg/m^3 (4.7 to 34.9 ppb). Additional results from this project are expected soon.

In public premises one European study is mentioned. In Germany, active sampling of indoor air was conducted for 4 hours during the main visiting hours in 28 premises in

the cities of Augsburg and Munich, from April 2005 to May 2006 (Bolte et al, 2008). Median levels of formaldehyde were 17 µg/m^3 (13.7 ppb) in restaurants and cafés (n=11), 17 µg/m^3 (13.7 ppb) in pubs and bars (n=7), and 47.0 µg/m^3 (37.9 ppb) in discotheques (n=10) (no smoke-free legislation).

Table 3.1.1.1. Indoor exposures to formaldehyde and attribution to sources (ordered by countries; large-scale studies are cited first and mentioned in bold characters)

STUDY	AM/sAMA (µg/m³)	GM/sGMB (µg/m³)	Median (µg/m³)	RangeC (µg/m³)	Data collection year	Type of buildings
GerES [1]						
Survey 1985/86	58.6	49.4/1.9		309 (max)		Homes
Survey 1991/92	79			816 (max)		Homes
Survey 2003/06	25.7	23.3	23.5	68.9 (max)	2003-2006	Homes (children's bedroom)
South Bavaria, Germany [22]				3.1-46.1	Winter 04-05 + summer 05	Schools
Germany [23]			28	76 (p95)	2001-2004	Offices
Augsburg and Munich,Germany [24]	14 (restaus) 23 (pubs) 47 (discos)		17 (restaurants) 17 (pubs) 47 (discos)	28 (restaurants) 63 (pubs) 86 (discos)	April 05-May 2006	Public premises
EXPOLIS [2]						
Helsinki		44.8	25.7	1.5-217.5	1996-1997	
OQAI [3] France			19.6 (18.4-21.0)	86.3 (max)	2003-2005	Homes (bedrooms)
Paris[4]		18.6/1.8	18,4	5% - 95%: 7.5 – 45.5		Homes of new-born
Strasbourg [25]	32.2/14.6				Feb.-May 04 + Oct. 04-May 05	Homes
6-cities, France [26]	27			4-100	1999	Schools

STUDY	AM/sAMA (µg/m³)	GM/sGMB (µg/m³)	Median (µg/m³)	RangeC (µg/m³)	Data collection year	Type of buildings
Strasbourg [27]	27 (primary) 22 (element.) 18 (day-care)		24 (primary) 20 (element.)	85 (primary) 80 (element.) 122 (day-care)	Nov. 04-Jan. 05	Schools and day-care centres
Rhône-Alpes Region, France [28]	24.1 (schools) 18.6 (day-care)			8.6-49 (schools) 7.3-41 (day-care)	June 06-March 07	Schools and day-care centres
Aarhus, Denmark[5]	37			- 290		Homes
Umeå, Sweden[6]	9			3 - 18		Offices
Borås, Sweden[7]	26/14		23	9.9 - 58		Homes (bedrooms)
Göteborg, Sweden[7]	35/22		29	8.6 - 120		Homes (bedrooms)
Uppsala, Sweden[8]		3/3.5		- 72		Schools
BRE (UK)		22,2	24	1-61.2-171		Homes
ALSPAC	25/21			1-205		Homes (main bedroom)
	23/17			1-181		Homes (living room)
AIRMEX						
All cities						Workplace[E]
						Homes
Brussels	13.9/5.6					Workplace[E]
	19.5/3.0					Homes
Budapest	18.2/6.8					Workplace[E]
	24.4/9.2					Homes
Leipzig	22.9/10.4					Workplace[E]
	18.6/13.4					Homes
Helsinki	19.7/9.8					Workplace[E]
	28.6/9.3					Homes
Arnhem	17.7/10.4					Workplace[E]
	30.7/17.8					Homes

STUDY	AM/sAMA (µg/m³)	GM/sGMB (µg/m³)	Median (µg/m³)	RangeC (µg/m³)	Data collection year	Type of buildings
Athens	20.5/8.8					Workplace[E]
	24.1/12.9					Homes
Catania	14.7/5.0					Workplace[E]
Dublin	17.5/13.3					Workplace[E]
	14.4/4.9					Homes
Nijmegen	19.5/6.8					Workplace[E]
	30.1/24.2					Homes
Thessaloniki	20.6/8.3					Workplace[E]
Belgium						
Flanders [29]	21 to 35					Homes
All Belgium [30]	18.1			4.1-103	March-June 2008	Day-care centres
Austria [31]			30	136 (max)	2006-2007	Schools
Other countries						
Japan[17]				91.25 -290		
UK[18]		22.2 (19.5 - 26.1)				
Australia[19]			15.8	139 (max)		
Louisiana, USA[20]				<LOQ[D]-6.6		
USA[21]				<LOQ[D]-575		

[A]AM = arithmetic mean and average concentration, sAM = standard deviation of arithmetic mean

[B] GM = geometric mean, sGM = standard deviation of geometric mean

[C] Range = minimum and maximum value

[D] LOQ = limit of quantification

E "workplace" = working environments (offices, classrooms, waiting halls) in public buildings, schools and kindergartens

[1] EXPOLIS 1999 and KUS, 2008; [2] Jurvelin et al. 2001; [3] Kircher et al. 2006; [4] Dassonville et al. 2009; [5] Harving et al. 1992; [6] Glas et al. 2004; [7] Gustafsson et al. 2005; [8] Smedje et al. 2001; [9] Raw et al. 2004; [10] Bruinen de Bruin et al. 2008; [11] INDEX 2005; [12] WHO 1989; [13] COMEAP 1997; [14] Jurvelin et al. 2001; [15] EPA/Cal 2003; [16] THADE 2004; [17] Minami et al. 2002; [18] Brown et al. 2002a; [19] Garret et al. 1999; [20] Lemus et al. 1998; [21] Liu et al. 1991; [22] Fromme et al, 2008; [23] BGIA, 2004; [24] Bolte et al, 2008; [25] Marchand et al, 2008; [26] Annesi-Maesano, 2001; [27] ASPA, 2005; [28] Rhône-Alpes, 2007; [29] VITO, 2007; [30] HVS, 2009; [31] LUKI, 2008

3.1.2 Hazard characterisation

Two studies on humans have been considered particularly relevant to characterise the hazard from formaldehyde.

One study was conducted on a group of 21 healthy volunteers exposed over a 2-week period to different continuous levels of formaldehyde in controlled conditions, with and without occurrences of concentration peaks, using a repeated exposure design (Lang et al., 2008). Each subject was exposed for 4 hours to each of the 10 exposure conditions on 10 consecutive working days. Eye irritation was found to be the most sensitive health outcome. Eye and nasal irritation were objectively observed at continuous exposure to 0.5 ppm with peaks of 1 ppm exposure, but not at constant exposure to 0.5 ppm. Effects reversed 16 hours after the end of the exposures. No significant effects on nasal flow and resistance, pulmonary function and reaction times were observed. It was concluded that a NOEL for subjective and objective eye irritation is 0.5 ppb in case of constant exposure levels, and 0.3 ppm with peaks of 0.6 ppm in case of short-term peak exposure.

Another study was conducted on asthmatic volunteers in controlled conditions to evaluate the influence of pre-exposure to low-dose formaldehyde (100 µg/m^3, 0.08 ppm, for 30 min) on bronchial response to a mite allergen (Casset et al. 2006). Subjects exposed to formaldehyde developed an immediate bronchial response at a significantly lower dose of mite allergen than after air exposure, suggesting that formaldehyde, in some way, might be involved in asthma exacerbation.

Concerning toxicity in animals, two studies in particular addressed the time-effect relationships of formaldehyde concentrations on airways.

In the first study (Nielsen et al. 1999), several irritation and respiratory parameters (such as air flow limitation or broncho-constriction patterns) in relation to formaldehyde exposure of the duration of 30 minutes were monitored in mice. A NOEL value of 0.3 ppm was established for sensory irritation from the `*just detectable effect*' (JDE) method described by authors. They deduced that at low concentrations adverse effects are due to trigeminal nerve stimulation.

In a more recent study (Andersen et al, 2008) rats were exposed to formaldehyde 6 hours per day, 5 days per week, up to 3 weeks. Endpoints considered included inflammatory infiltrate, epithelial hyperplasia and genomic signature in nasal epithelial tissues of rats. Inflammatory response was observed starting from 0.7 ppm (LOAEL), while a trend toward altered gene expression was observed between 0.7 and 2 ppm. As regards cell proliferation no effect was found below 2 ppm.

Documents published by international institutions are summarised and reviewed in Appendix D, Table A, while in Appendix D, Table B a summary of the most significant effects due to exposure to formaldehyde on humans and animals (excluding carcinogenicity) is reported.

3.1.3 Exposure Reference Values

The proposal for reference exposure levels has been based on the three study chosen as pivotal (one on humans and two on animals), by applying safety factors chosen according to WHO/IPCS (IPCS, 2006) to the identified relevant endpoints. The choice of the Chemical Specific Assessment Factor (CSAF) has been based on several assumptions.; Humans have lower target tissue exposure to the substance than rodents that are nose-only breathers. Nevertheless, it may be that the effects of the substance on the nose of rodents have a predictive value for effects in humans on more distal parts of the respiratory tract, such as larynx, bronchi, and lungs (Casanova et al, 1991) thus, in the calculation of reference value a CSAF of 1 has been assigned to formaldehyde.

Study No. 1	***Nielsen et al., 1999***
Study population	Male BALB/cA mice (n=32; 4 per exposure group).
Exposure	Mice were inserted into body plethysmographs connected to the exposure chamber; exposure concentrations of formaldehyde were from 0.2 to 13 ppm. Duration of exposure was 30 minutes.
Critical effects	Sensory irritation parameters; air flow limitation or broncho-constriction patterns.
Endpoint considered	Sensory irritation
NOEL	0.3 ppm.
Uncertainty factor	**3.16**
Comment	Being mice nose-only breathers, humans are supposed to have lower target tissue exposure to the active chemical moiety for the same external dose. Thus, no uncertainty factor has been considered for interspecies variability. An uncertainty factor of 3.16 for intra-species toxicodynamic only has been applied, assuming that effects here considered are local and do not involve toxicokinetics.
Reference value	**0.095 ppm (≈120 µg/m^3)**

Study No. 2	***Andersen et al., 2008***
Study population	Rats (n=8 per group, per time-point)
Exposure	Inhalation chamber, 6 h/day, 5d/week, up to 3 weeks. Exposure groups: 0.7, 2, 6 and 15 ppm.
Critical effects	Nasal mucosa: inflammatory infiltrate, epithelial hyperplasia, gene changes (squamous metaplasia, cell proliferation at higher concentrations)
Endpoint considered	Inflammatory infiltrate
LOAEL	0.7 (measured 0.6) ppm
Uncertainty factor	**3 X 3.16 = 9.48**
Comment	Being mice nose-only breathers, humans are supposed to have lower target tissue exposure to the active chemical moiety for the same external dose. Thus, no uncertainty factor has been considered for interspecies variability. An uncertainty factor of 3.16 for intra-species toxicodynamics has been applied, assuming that effects here considered are local and do not involve toxicokinetics, multiplied for the adjustment factor of 3 for the use of a LOAEL.
Reference value	**0.074 ppm (≈90 µg/m^3)**

Study No. 3	***Lang et al., 2008***
Study population:	21 healthy volunteers (11 males, 10 females)
Exposure	Repeated measure design; each person exposed to both constant and peak levels for 4h and 10 consecutive days in 10 different exposure conditions.
Critical effects	Eye irritation (conjunctival redness, blinking frequency), nasal flow and resistance, pulmonary function and reaction times.
Endpoint considered	Eye irritation
LOAEL	0.5 ppm with 1 ppm peaks
NOAEL	0.5 ppm constant level (or 0.3 ppm with 0.6 ppm peaks)
Uncertainty factor	**3.16**
Comment	An uncertainty factor of 3.16 for intra-species toxicodynamic only has been applied, assuming that effects here considered are local and do not involve toxicokinetics.
Reference values	**0.158 ppm (≈ 200 µg/m^3) constant level** **0.095 ppm (≈ 120 µg/m^3) with peaks (0.190 ppm- ≈ 235 µg/m^3)**

Based on objective eye irritation, the reference value proposed for short-term exposure to formaldehyde is in the range of 70-100 ppb (90-120 µg/m^3).

3.2 Exposure characterisation and Exposure Scenarios in hospitals

3.2.1 Uses and exposure determinants identified

Based on the operational conditions observed during the first inspection at Pathology Unit of University Hospital L. Sacco and, taking into account exposure determinants, 6 tasks have been identified as critical for formaldehyde exposure:

1. Formalin dilution to operational concentration;
2. Specimens dissection;
3. Inclusion of specimens into containers (dissection room);
4. Inclusion of specimens into containers (central lab);
5. Disposal (pouring);
6. Disposal (rinsing).

Table 3.2.1.1 reports the critical tasks and exposure determinants identified at Pathology Unit of University Hospital L. Sacco are reported. Mitigation measures in place at the time of the survey are also reported.

Table 3.2.1.1 Potentially critical tasks that entail use of formalin identified at University Hospital L. Sacco

Task/Use	Description	Environment (room)	Concentration & Quantity	Frequency	Duration	Mitigation measures
1. Formalin dilution	Formalin is diluted into distilled water to operational condition.	Dissection room (B).	From 30 to 4% m/v formaldehyde solution; V: 10 L.	Twice a week.	Few minutes.	Ventilated bench.
2. Specimens dissection	Specimens coming from other units, already put in formalin, are cut into thinner sections or sampled for suitable pieces.	Dissection room (B).	4% m/v formaldehyde solution; V: 10 times specimen volume.	Daily.	Several hours.	Ventilated bench.
3. Specimens inclusion (1)	Specimens (high volume) are placed into containers and filled with formalin	Dissection room (B).	4% m/v formaldehyde solution; V: 10 times specimen volume (up to several L).	Daily.	NQ[1] (probably few minutes)	Ventilated bench.

Task/Use	Description	Environment (room)	Concentration & Quantity	Frequency	Duration	Mitigation measures
4. Specimens inclusion (2)	Specimens (biopsies) are placed into bio-cassettes and filled with formalin	Central lab (A)	4% m/v formaldehyde solution; V: 10 times specimen volume (<10 mL/container).	Daily.	~30 minutes.	Chemical hood.
5. Pouring	Residual formalin present in containers is poured into apposite sink	Dissection room (B).	4% m/v formaldehyde solution; V: 10 times specimen volume (up to several L)..	Daily	Few minutes.	Ventilated bench.
6. Rinsing	Recyclable containers are washed under tap water	Washing room (Z)	4% m/v formaldehyde solution V: NQ[1]	Almost daily.	Few minutes.	None (no ventilation, no windows).

[1]NQ: not quantifiable.

The second hospital investigated, being a Cancer Institute, has a larger Pathology Department, divided into three sections (two dedicated to routine pathology and one to research). Direct uses of formalin, which are identified as critical, have been described and reported in table 3.2.1.2.

Table 3.2.1.1 Potentially critical tasks that entail use of formalin identified at National Cancer Institute.

Task/Use	Description	Environment (room)	Concentration & Quantity	Frequency	Duration	Mitigation measures
1. Specimens dissection (1)	Fresh[1] organs coming from other units are cut into thinner sections.	Dissection room (A)	4% m/v formaldehyde solution; V= up to 20 L for big organs,	Daily	Several hours	Chemical hood (kept switched on for 1 our after operation has finished)
2. Specimens dissection (2)	Biopsies coming from other units, already put into formalin, are sampled for suitable pieces.	Dissection room (A)	4% m/v formaldehyde solution; V= 10 mL	Daily	Several hours	Chemical hood (kept switched on for 1 our after operation has finished)
3. Specimens inclusion	Formalin is poured into the containers through the opening of a tap.	Dissection room (A)	4% m/v formaldehyde solution; V= up to 20 L for big organs, 10 mL for biopsies;	Daily	Several minutes	Chemical hood

4. Biopsy positioning	Small dimension biopsies already included in formalin, are put into bio-cassettes.	Processing room (B)	4% m/v formaldehyde solution; V= 10 mL.	Daily	~ 1 hour	Chemical hood
5. Formalin upload and download	Formalin is uploaded and downloaded from processing machine.	Processing room (B)	4% m/v formaldehyde solution; V= 5 tanks of 5 L, total: 10 L.	1-2 times per day	~15 minutes	Exhaust ventilation: 20 air exchange per hour (theoretical).
6. Bio-cassettes upload and download	Bio-cassettes are positioned inside formalin in the processing machine.	Processing room (B)	4% m/v formaldehyde solution; V: 10 L.	2 upload & download per day for each machine (total: 8 times/day)	Few minutes	Exhaust ventilation: 20 air exchange per hour (theoretical).
7. Pouring	Residual formalin present in containers is poured into apposite sink.	Dissection room (A)	4% m/v formaldehyde solution; V= 10 mL.	Daily	Few seconds per container	Chemical hood
8. Disposal of archive specimens	Residual formalin present in big, containers of archive is poured into apposite sink.	Disposal room (C)	4% m/v formaldehyde solution; V = up to 20 L.	Almost daily	Up to 1 hour.	Chemical hood
9. Rinsing	Recyclable containers are washed under tap water	Disposal room (C)	4% m/v formaldehyde solution V: NQ[2]	Almost daily	Few minutes	Chemical hood
10. Washing	Recyclable containers are put inside washing machine	Ex-autopsy room (D)	4% m/v formaldehyde solution V: NQ[2]	Almost daily	Few minutes	None

[1] Fresh: not included in formalin

[2] NQ : not quantifiable

Due to working organisation and timing it has not been possible to carry out any sampling for some of the tasks. Sometimes two or more tasks have been monitored at the same time. Further, some other situations or tasks identified as potentially non-critical have been monitored as described in paragraph 3.2.3.

3.2.2 Preliminary measurements

A screening monitoring at University Hospital L. Sacco has been conducted with passive method Dräger Bio-check-F during the first visit at Pathology Unit. 2 hours TWA of formaldehyde air concentrations have been measured in three environments:

1. Central lab (Room A): during various tasks which do not involve direct use of formalin such inclusion into paraffin, colouration, sorting and labelling. Less than usual activity has been reported.
2. Dissection room (room B): during organ dissection.
3. Archive, located in the basement (room C), where numerous specimens are archived in containers.

Another sampler has been pinned on an operator during her routine activity, which has been performed in central lab mostly. Reportedly less than usual work has been carried out that day.

Outcomes of the preliminary monitoring survey are reported in table 3.2.2.1.

Table 3.2.2.1 Outcomes of the preliminary monitoring at University Hospital L. Sacco.

Sample	Room	Time	Class	Concentration range	Observations
1	Archive at the basement (C)	11.37 – 13.37	**C**	**0.1 - 0.2 ppm**	No activity.
2a	Central lab (A)	11.46 – 13.46	**B**	**0.05 - 0.1 ppm**	Various “indirect” tasks
2b	Central lab (A)	12.53 – 14.53	**B**	**0.05 - 0.1 ppm**	Various “indirect” tasks
3	On operator in central lab (A)	11.43 – 13.43	**B**	**0.05 - 0.1 ppm**	Various “indirect” tasks
4a	Dissection room (B)	11.48 – 13.48	**E**	**≥ 0.3 ppm**	Cutting of a big organ
4b	Dissection room (B)	12.52 – 14.52	**E**	**≥ 0.3 ppm**	No activity

3.2.3 Monitoring survey at University Hospital L. Sacco

The monitoring has been conducted in July 2010, during routine activity of the Pathology Unit. Tasks monitored with 3 techniques have been:

1. Specimens dissection and inclusion into formalin in dissection room (including cutting of large organs);
2. Various tasks not involving the direct use of formalin such as specimens processing, inclusion into paraffin, colouration, microtome sectioning and specimens sorting in central lab;
3. Formalin dilution in dissection room;
4. Specimens inclusion in central lab (small biopsies);
5. Pouring of residual formalin in dissection room (5 high volume containers up to 5 L).

Other environments have been monitored with passive sampler Bio-check F and/or photo-acoustic gas monitor. On personnel request, one Bio-check F measurement has been performed in the cellar where archives are stored (situation no. 6). A task identified as critical, rinsing of recyclable containers, could not be performed because no used containers were present that day, nevertheless a measurement with photo-acoustic and Bio-check has been carried out while rinsed containers were drying (situation no. 7). Both environments (cellar and washing room) are not provided with any ventilation system.

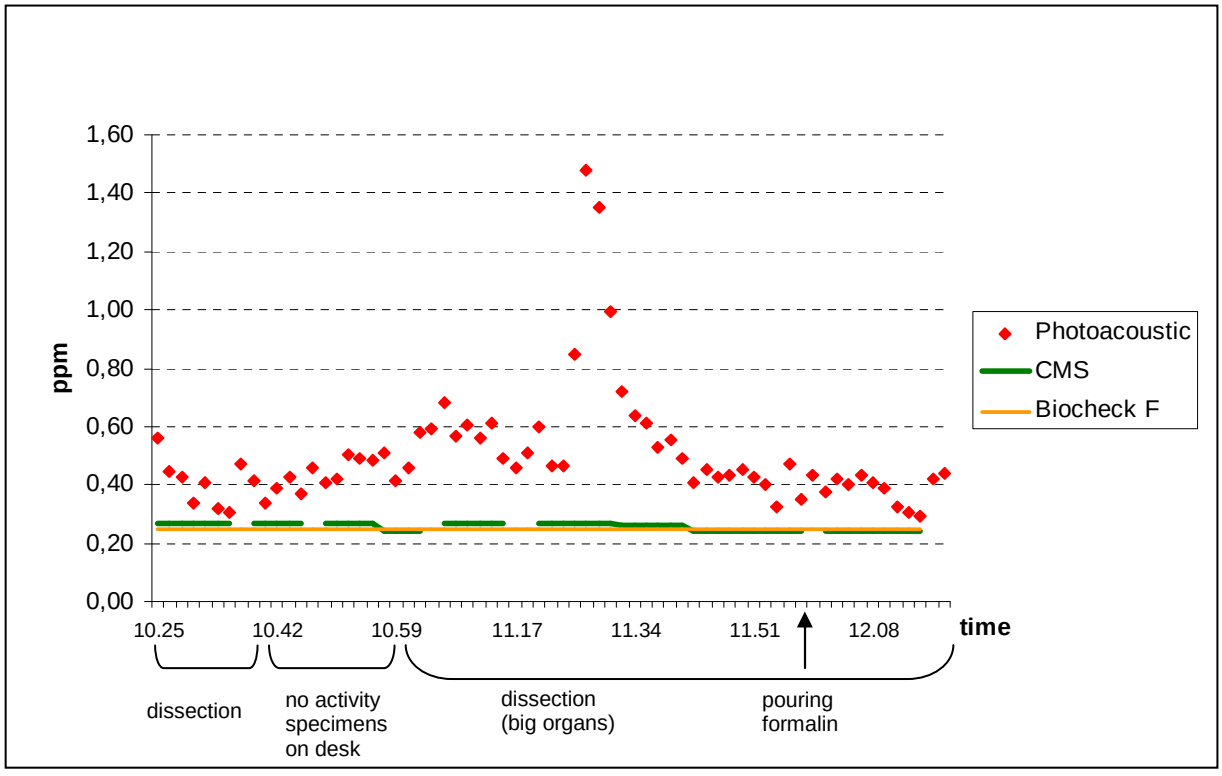
Data and charts depicting relevant outcomes are presented in this section. Relevant occurrences observed during measurements are reported in charts.

During situation no. 1 (specimens dissection and inclusion into formalin) formaldehyde concentrations detected have been:

- Photo-acoustic: maximum 1.48 ppm; mean 0.5 ppm (n=67);
- CMS: maximum 0.27; mean 0.26 ppm (n=11);
- Bio-check F: class D (0.2-0.3 ppm).

The peak of concentration detected occurred during cutting of a large organ, and no particular occurrence has been observed.

Chart 3.2.3.1 Specimens dissection and inclusion into formalin in dissection room (Pathology Unit, University Hospital L. Sacco)

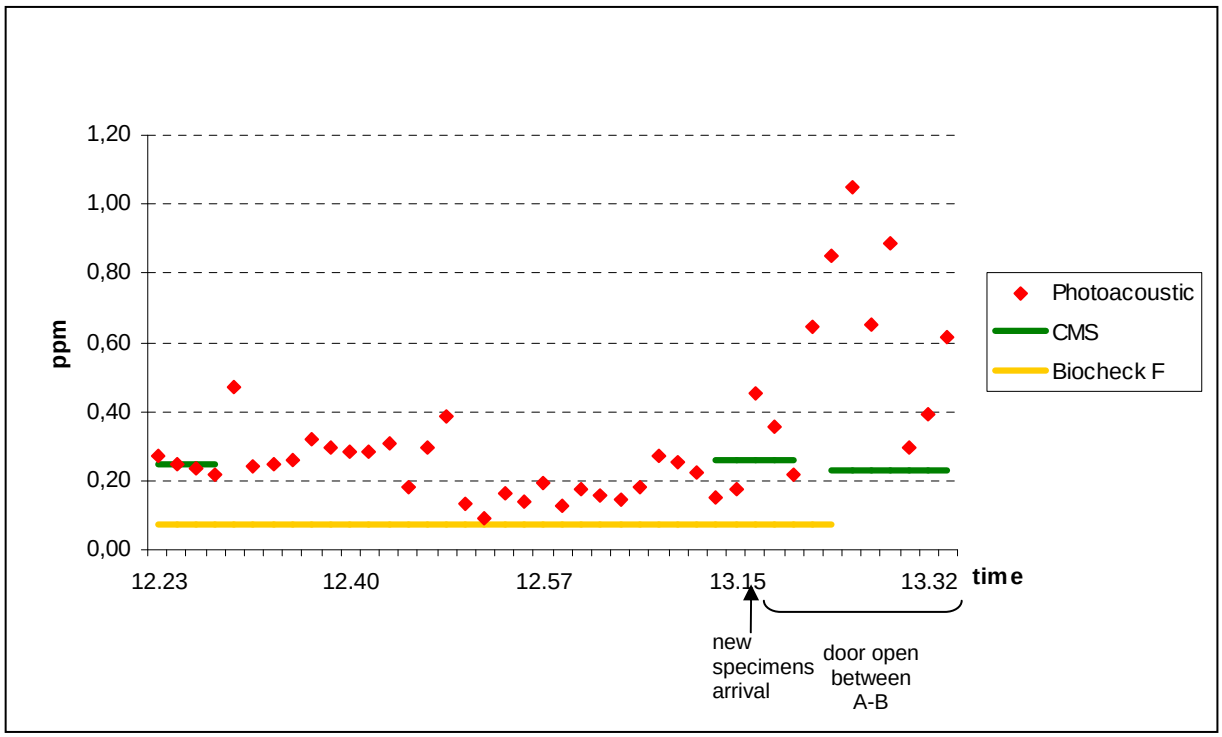


During situation no.2 (various “indirect” tasks in central lab) concentrations detected have been:

- Photo-acoustic: maximum 1.05 ppm; mean 0.32 ppm (n=42);
- CMS: maximum 0.26 ppm; mean 0.24 ppm (n=3);
- Bio-check F: class B (0.05-0.1 ppm).

As depicted in chart 3.2.3.2, a peak of concentration is to be noted. It has been detected after the arrival of new specimens already included in formalin left on a desk (not under chemical hood). At the same time, the door left open between central lab and dissection room has been observed.

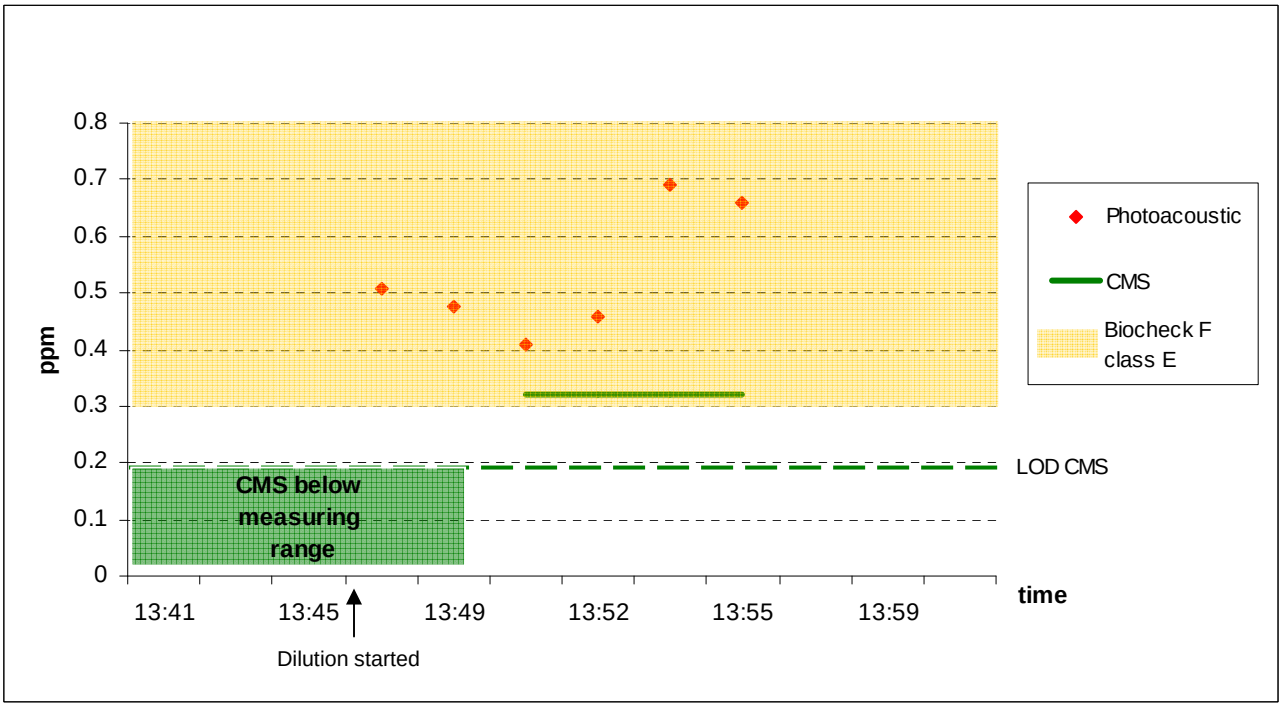
Chart 3.2.3.2 Various tasks in central lab (Pathology Unit, University Hospital L. Sacco)



During situation no. 3 (formalin dilution in dissection room) concentrations detected have been:

- Photo-acoustic: maximum 0.69 ppm; mean 0.53 ppm (n=6);
- CMS: maximum 0.32 ppm, mean 0.24 ppm (n=2); 1 measurement has been below LOD (0.2 ppm); it started before the operation beginning and ended during task.
- Bio-check F: class E (≥0.3 ppm).

Chart 3.2.3.3 Formalin dilution in dissection room (Pathology Unit, University Hospital L. Sacco)

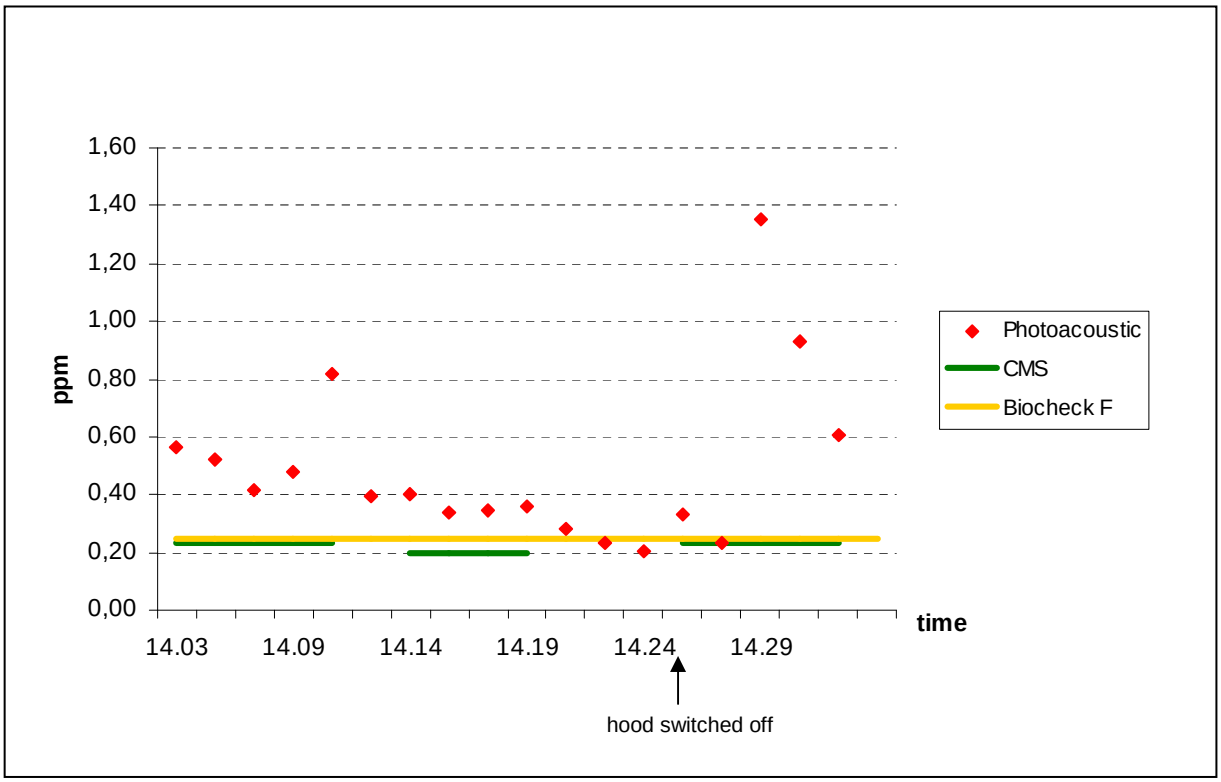


During situation no. 4 (biopsies inclusion into formalin in central lab) concentrations detected have been:

- Photo-acoustic: maximum 1.35 ppm; mean 0.49 ppm (n=18);
- CMS: maximum 0.23 ppm, mean 0.22 ppm (n=3);
- Bio-check F: class D (0.2-0.3 ppm).

To be noted, as depicted in chart 3.2.3.4, the peak concentration detected just after the chemical hood has been switched off.

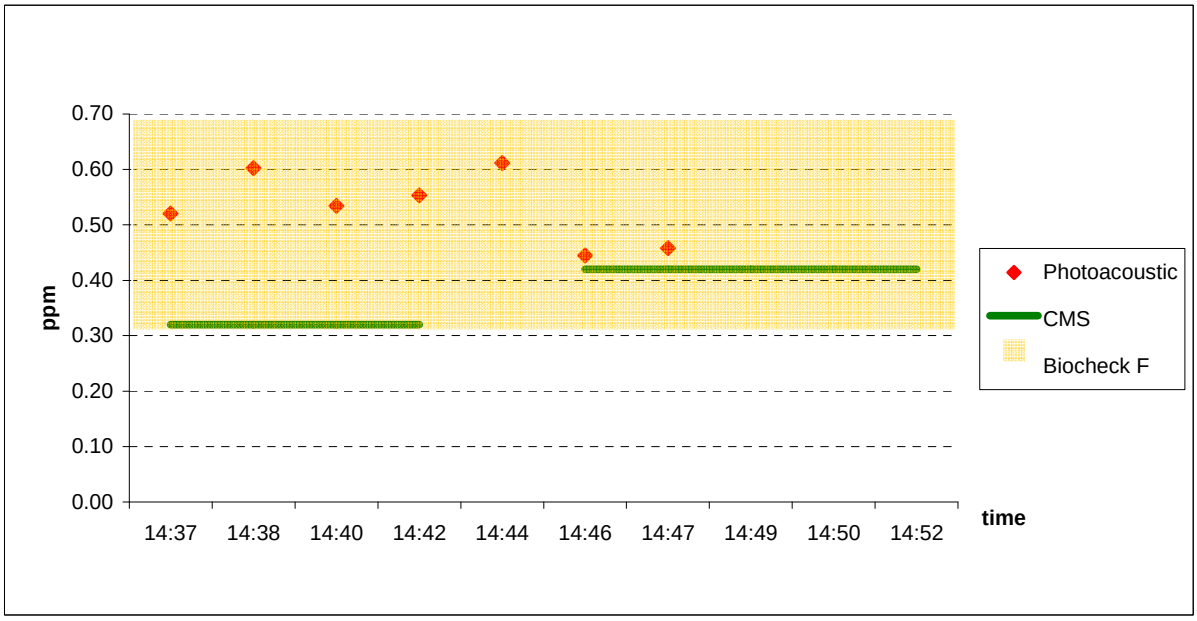
Chart 3.2.3.4 Biopsies inclusion into formalin in central lab (Pathology Unit, University Hospital L. Sacco)



During situation no. 5 (disposal: pouring residual formalin in dissection room) concentrations detected have been:

- Photo-acoustic: maximum 0.61 ppm; mean 0.53 ppm (n=7);
- CMS: maximum 0.42 ppm, mean 0.38 ppm (n=2);
- Bio-check F: class E (≥0.3 ppm).

Chart 3.2.3.5 Formalin disposal in dissection room (Pathology Unit, University Hospital L. Sacco)



Results of other environments monitored are reported in table 3.2.3.1

Table 3.2.3.1 Other environments monitored at Pathology Unit, University Hospital L. Sacco

Situation	Environment	Formaldehyde levels		Notes
		Bio-check F	Photo-acoustic	
6. Specimen archives	Basement (room C)	Class E (≥ 0.3ppm)	-	Organs kept in non-hermetic bins
7. Washing	Washing room (room Z)	Class B (0.05 - 0.1ppm)	Below detection limit (0.04 ppm)	No activity; containers left to dry.

The maximum concentration detected has been 1.48 ppm (photo-acoustic monitor) during specimens dissection and inclusion into formalin in dissection room (room B). Peak concentrations above 1 ppm have been detected by the photo-acoustic monitor in three situations (no.1, no.2, no.4, dissection, biopsies inclusion and during various, "indirect", operations respectively).
Summary data of the air monitoring at University Hospital L. Sacco are reported in table 3.2.3.2

Table 3.2.3.2 Summary data of University Hospital L. Sacco monitoring

Task/situation	**Environment**	**Photo-acoustic (ppm)**		**CMS (ppm)**		**Bio-check F (ppm)**
		Max	**Average**	**Max**	**Average**	**2 hrs TWA**
No. 1	Room B	1.48	0.5	0.27	0.26	≥ 0.3
No. 2	Room A	1.05	0.32	0.27	0.24	0.05-0.1
No. 3	Room B	0.69	0.53	0.32	0.24	≥ 0.3
No. 4	Room A	1.35	0.49	0.23	0.22	0.2-0.3
No. 5	Room B	0.61	0.53	0.42	0.38	≥ 0.3
No. 6	Room C	-	-	-	-	≥ 0.3
No. 7	Room Z	< LOD	-	-	-	0.05-0.1

3.2.4 Monitoring survey at National Cancer Institute

The monitoring has been conducted at the end of October 2010, during routine activity of the Pathology Unit. Situations monitored with at least two techniques have been:

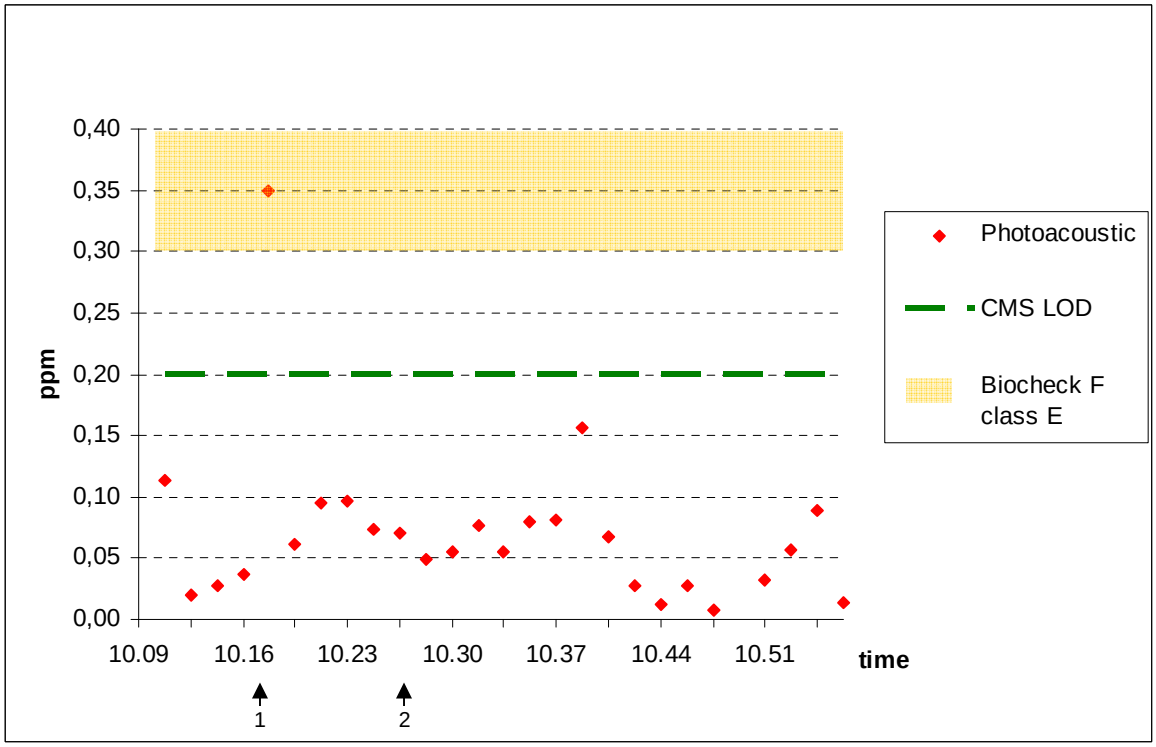
1. Specimens dissection (2): sampling of biopsies and inclusion into formalin (tap of formalin tank opened several times) in dissection room;
2. Formalin upload and download in processing room;
3. Specimens dissection (1): cutting of “fresh” organs (not already included into formalin) and inclusion into formalin in dissection room;
4. Disposal of archive specimens (pouring residual formalin) in disposal room;
5. Washing of recyclable containers in ex autopsy room (CMS and Bio-check F only);
6. Biopsies positioning in processing room;
7. Bio-cassettes upload and download in processing room (photo-acoustic and CMS);
8. Pouring of residual and loading of new formalin in dissection room (photo-acoustic and CMS).

Data and charts depicting relevant outcomes are presented in this section. Relevant occurrences observed during measurements are reported in charts.

During situation no. 1 (biopsies sampling and inclusion into formalin) formaldehyde concentrations detected have been:

- Photo-acoustic: maximum 0.35 ppm; mean 0.07 ppm (n=27);
- CMS: below LOD (0.2 ppm; n=5)
- Bio-check F: class E (≥ 0.3 ppm).

Chart 3.2.4.1 Biopsies sampling and inclusion into formalin (Pathology dept. National Cancer Institute)



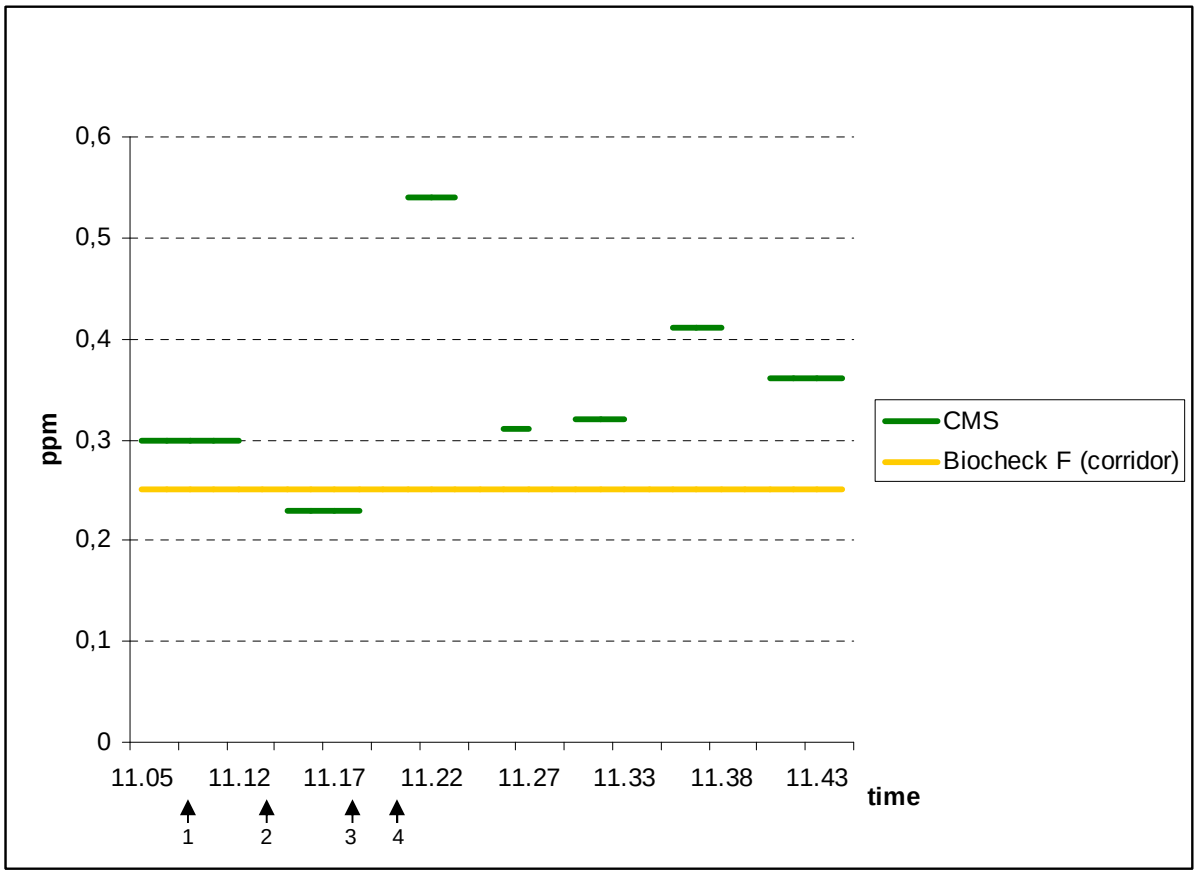
1. Observation no. 1: operator passed above instruments with gloves soaked with formalin

2. Observation no. 2: formalin tank opened for 1 min ca.

In situation no. 2, formalin upload and download in processing room, photo-acoustic measurements have been invalidated because of positive interferences present in the room (ethanol and xylenes), thus cannot be used to depict formaldehyde levels. Concentrations detected with other two methods have been:

- CMS: maximum 0.54 ppm, mean 0.35 ppm (n=2);
- Bio-check F in processing room: null measurement;
- Bio-check F positioned in the corridor, in front of the door between processing room (left open): class D (0.2- 0.3 ppm).

Chart 3.2.4.2 Formalin upload and download in processing room (Pathology dept. National Cancer Institute)



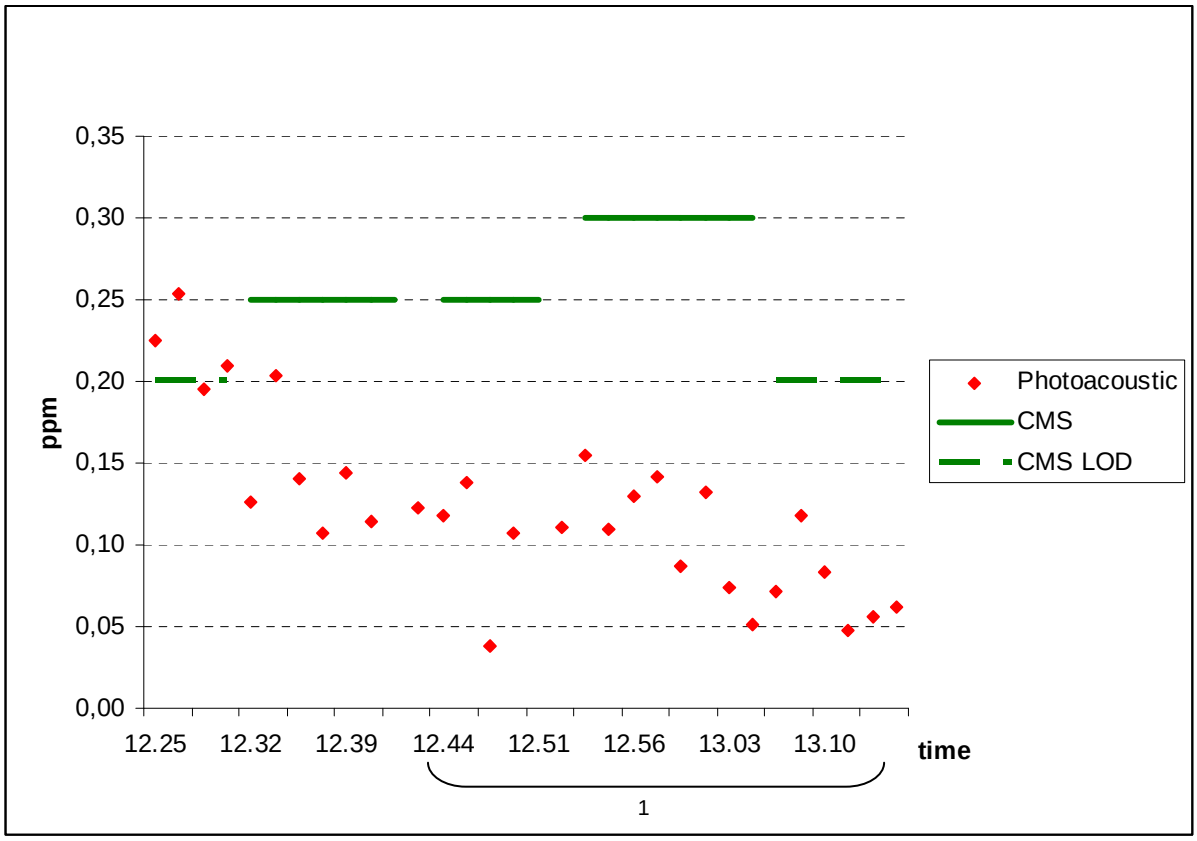
1. Observation no. 1: download started.
2. Observation no. 2: automatic upload started (1st tank).
3. Observation no. 3: manual upload started (2nd tank).
4. Observation no. 4: accidental pouring on the floor.

During situation no. 3, cutting of organs, not already included into formalin (specimens dissection 1) and inclusion into formalin in dissection room formaldehyde concentration detected have been:

- Photo-acoustic: maximum 0.25 ppm; mean 0.12 ppm (n=30);
- CMS: maximum 0.3 ppm; mean 0.24 (n=5); 2 measurements below LOD (0.2 ppm);
- Bio-check F: class E (≥ 0.3 ppm).

As Bio-check F sampler has been applied on an operator (operator no.1) which has carried out assistance to the pathologist which performed these tasks. The operator has also opened the formalin tank many times. Due to the different purpose of measurement (personal vs environmental sampling) concentration detected is not comparable to those of photo-acoustic and CMS sampler, thus it has not been reported in the same chart.

Chart 3.2.4.3 Organs cutting and inclusion into formalin in dissection room (Pathology dept. National Cancer Institute)

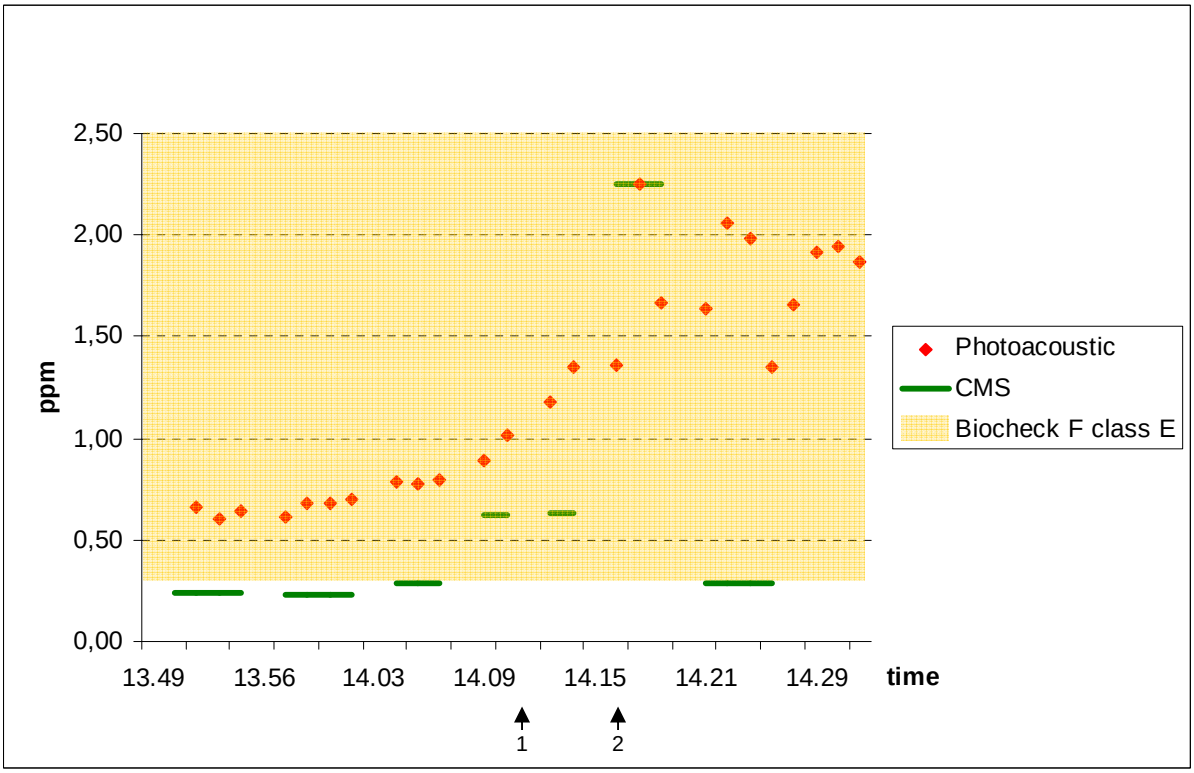


1. Observation no. 1: High volume containers of formalin (5 L ca.) left open under chemical hood

During situation no. 4, disposal of archive specimens (pouring residual formalin) in disposal room formaldehyde concentration detected have been:

- Photo-acoustic: maximum 2.25 ppm; mean 1.24 ppm (n=25);
- CMS: maximum 2.25 ppm; mean 0.60 (n=7);
- Bio-check F: class E (≥ 0.3 ppm).

Chart 3.2.4.4 Archives disposal: pouring of residual formalin in disposal room (Pathology dept. National Cancer Institute)



1. Observation no. 1: accidental pouring on the floor.
2. Observation no. 2: strong, suffocating odour, monitoring work team left the room.

During situation no. 5, washing of recyclable containers in ex autopsy room formaldehyde concentration have been detected with CMS and Bio-check F only:

- CMS: maximum 0.26 ppm; mean 0.25 (n=2);
- Bio-check F: class D (0.2-0.3 ppm).

Due to few, short-time, data collected, related chart has not been reported since it does not add any supportive information.

During situation no. 6, biopsies positioning in bio-cassettes in processing room, photo-acoustic measurements have been invalidated because of positive interferences present in the room (ethanol and xylenes), as well as in situation no.2. Concentrations detected with other two methods have been:

- CMS: maximum 0.29 ppm; mean 0.25 (n=4);
- Bio-check F: class E (≥ 0.3 ppm).

In this case also, due to few, short-time, data collected, related chart has not been reported since it does not add any supportive information.

Situation no. 7, bio-cassettes upload and download in processing room, has been characterised by the presence of positive interferences too (for photo-acoustic). Bio-check F sampler has not been considered worthy to use because of the brevity of the task. Thus, only data from CMS are reported:

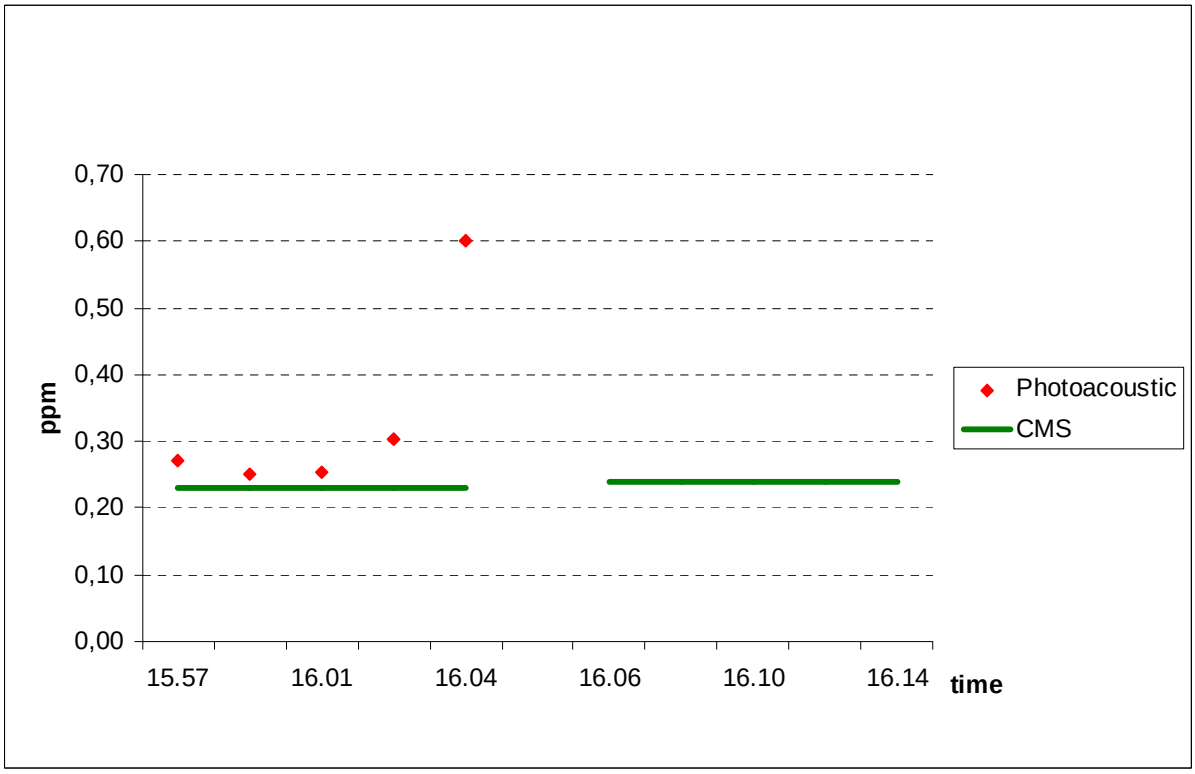
- CMS (1 measurement): 0.3 ppm

Chart is not reported.

During situation no. 8, pouring of residual and loading of new formalin in dissection room, concentration of formaldehyde have been detected with photo-acoustic monitor and CMS sampler only. Bio-check F sampler has not been considered worthy to use because of the brevity of the task. Outcomes have been:

- Photo-acoustic: maximum 0.6 ppm; mean 0.34 ppm (n=5).
- CMS: maximum 0.24 ppm; mean 0.24 ppm (n=2)

Chart 3.2.4.5 Pouring residual and loading new formalin in dissection room (Pathology dept. National Cancer Institute)



Other environments, i.e. rooms where there is not a direct use of formalin, have been monitored with passive sampler Bio-check F. Personal monitoring have been also carried out with Bio-check F sampler on four operators involved in different tasks. All Bio-check F measurements reported levels in class E (≥0.3 ppm) as reported in table 3.2.4.1

Table 3.2.4.1 Various situations and environments monitored with Bio-check F at National Cancer Institute.

Sample	Environment	Time	Tasks carried out during monitoring	Class	Formaldehyde concentrations (ppm)
1	Dissection room (space 1)	10.10-12.10	Biopsies sampling, opening of formalin tank.	E	≥0.3
2	Dissection room (space 2)	10.10-12.11	Various; no biopsies sampling	C	0.1-0.2
3	Corridor A (next to dissection room)	10.18-12.18	Passageway	A	≤0.05
4	Cytology lab	10.18-12.18	Various/not specified	B	0.05-0.1
5	Secretary office A (small room)	10.22-12.22	Secretary activities	A	≤0.05
6	Experimental Molecular Pathology lab	10.24-12.24	Various/not specified	A	≤0.05
7	Diagnostic Molecular Pathology lab	10.24-12.24	Various/not specified	B	0.05-0.1
8	Processing room	11.05-13.05	Formalin upload and download from processing machines	Null	-
9	Corridor B (in front of processing room)	11.15-13.15	Passageway; door open between corridor and processing room during upload/download	D	0.2-0.3
10	Paraffin and colouration lab	11.20-13.20	Various/not specified	B	0.05-0.1
11	Histology lab	11.32-13.32	Personnel meeting	B	0.05-0.1
12	Operator 1: dissection room	12.40-14.40	Assistance to sampling and cutting; formalin tank opening.	E	≥0.3
13	Operator 2: processing room	13.00-15.00	Formalin upload and download from processing machines	E	≥0.3
14	Ex autopsy room	13.10-15.10	Loading of containers into washing machines; washing cycle; drying of containers	D	0.2-0.3
15	Disposal room	13.10-15.10	Pouring of residual formalin (ca. 15 big containers 2-3 L and 20 small 250 mL)	E	≥0.3
16	Secretary office B (large room)	13.25-15.25	Secretary activities	B	0.05-0.1

Sample	Environment	Time	Tasks carried out during monitoring	Class	Formaldehyde concentrations (ppm)
17	Processing room	13.35-15.35	Positioning of small biopsies in bio-cassettes	E	≥0.3
18	Immune-histo-chemistry lab	13.35-15.35	Various/not specified	B	0.05-0.1 (media 0.075)
19	Corridor B (in front of processing room)	13.37-15.37	Positioning of small biopsies in bio-cassettes in processing room (door open)	Null	-
20	Operator 3: disposal room, ex autopsy room;	13.52-15.52	Archives disposal (pouring formalin), loading washing machines	E	≥0.3
21	Operator 4: processing room	14.55-rimozione	Positioning of small biopsies in bio-cassettes	Null	-

The maximum concentration detected in monitoring survey has been 2.25 ppm (found with both photo-acoustic and CMS methods) during pouring of residual formalin in disposal room (room C), the only task/situation to produce peak concentrations above 1 ppm. In three situations (no. 2, 6, 7) photo-acoustic measurements gave very high peak concentrations, but have been discarded because of the presence of positive interferences inside processing room. Summary data of the air monitoring at National Cancer Institute are reported in table 3.2.4.2.

Table 3.2.4.2 Summary data of National Cancer Institute monitoring

Task/circumstance monitored	Environment	Photo-acoustic (ppm)		CMS (ppm)		Bio-check F (ppm)
		Max	Average	Max	Average	2 hrs TWA
No. 1	Room A	0.35	0.07	< LOD	-	≥ 0.3
No. 2	Room B	Dis[1]	Dis[1]	0.54	0.35	0.2-0.3
No. 3	Room A	0.12	0.25	0.3	0.24	≥ 0.3 (operator)
No. 4	Room C	2.25	1.24	2.25	0.65	≥ 0.3
No. 5	Room D	-	-	0.26	0.25	0.2-0.3
No. 6	Room B	Dis[1]	Dis[1]	0.29	0.25	≥ 0.3
No. 7	Room B	Dis[1]	Dis[1]	0.3	0.3	-
No. 8	Room A	0.6	0.34	0.24	0.24	-

[1]Dis: discarded because of positive interferences.

3.2.5 Exposure Scenarios and Risk Management Measures proposal

Exposure Scenario development has been based on REACH Regulation Guidelines, particularly on the document *"Guidance on information requirements and chemical safety assessment - Part D: Exposure Scenario Building"* (ECHA, 2008). First, a checklist has been completed during the personnel interviews and the inspection of laboratories. To answer some questions, the support of the Prevention and Protection Service of both hospitals has been required.

Always basing the Scenario development on REACH Technical Guidance, an exposure estimation model has been taken into account and, as exercise, tested on a generic task repeated several times per day in a pathology laboratory (see Appendix A). The concentration estimated are in the same order of magnitude of those encountered during the surveys and the detailed results of exposure modelling; the model description and the input/output data are reported in Appendix A.

Exposure data obtained from air monitoring surveys have been evaluated and implemented into the Exposure Scenario. Concentration values exceeding TLV-C for formaldehyde (0.3 ppm) have been highlighted, trying to describe possible causes of exceeding formaldehyde levels. Further, Risk Management Measures (RMMs) for each task resulting in a potential risk for operators health have been proposed.

Exposure Scenarios developed are presented in a re-arranged format based on REACH guidelines. An Exposure Scenario can pool more than one task together. This is the case when two or more task are carried out at the same time and in the same environment, where the single source of emission is not distinguishable during a routine work activity (i.e specimens dissection and inclusion into formalin). Also various, indirect, tasks performed in the same environment where a relevant, single source of formaldehyde is not expected, have been grouped in the same Exposure Scenario.

University Hospital L. Sacco

Among tasks and situations monitored (7), five of them presented formaldehyde levels clearly exceeding the TLV-C, (situations no 1, 2, 3, 4 and 5). Thus, five Exposure Scenarios have been developed and presented to the Prevention and Protection Service of the Hospital.

Exposure Scenario no. 1

Scenario name	***Specimens dissection and inclusion into formalin***		
Task description	Specimens coming from other units, already put in formalin, are cut into thinner sections or sampled for suitable pieces which are placed into containers and filled with formalin.		
Exposure determinants			
Environment	Dissection room (room B)		
Concentration	4% m/v formaldehyde solution		
Quantity	10 times specimen volume (up to several L)		
Duration	Several hours		
Frequency	Daily		
Existing mitigation measures	Ventilated bench		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 1.48 ppm; Average: 0.5 ppm;	Max: 0.27 ppm	class D (0.2-0.3 ppm)
TLV exceeded	**YES**	NO	NO
Causes identified for exceeding concentrations	- Poor exhaust ventilation (no chemical hood). - Very small room size (2 operators can hardly work).		
Proposed Risk Management Measures			
1. Re-arrange rooms and working spaces: functional to tasks.			
2. Provide effective exhaust chemical hood.			
3. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

Exposure Scenario no. 2

Scenario name	***Various tasks (indirect)***		
Task description	Several routine operations, which do not involve the direct use of formalin such as processing, inclusion into paraffin, colouration, microtome sectioning and specimens sorting.		
Exposure determinants			
Environment	Central lab(room A)		
Concentration	4% m/v formaldehyde solution		
Quantity	NQ[1]		
Duration	Task dependent		
Frequency	Daily		
Existing mitigation measures	Chemical hoods (6)		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 1.05 ppm; Average: 0.32 ppm;	Max: 0.27 ppm	class B (0.05-0.1 ppm)
TLV exceeded	**YES**	NO	NO
Causes identified for exceeding concentrations	- Specimens included in formalin, and probably not sealed, left on a bench (no hood). - Door left open between room A and B (dissection room).		
Proposed Risk Management Measures			
1. Provide general safety indication to all personnel of the Unit (i.e. close doors, do not leave formalin containers outside hoods, ventilated benches or cupboards).			
2. Avoid misuses, providing task-specific training to personnel involved (i.e. moving specimens)			

[1]NQ: not quantifiable.

Exposure Scenario no. 3

Scenario name	***Formalin dilution***		
Task description	Formalin, provided in tanks from Pharmacy Unit, is diluted to operational condition into distilled water.		
Exposure determinants			
Environment	Dissection room (room B)		
Concentration	From 30 to 4% m/v formaldehyde solution		
Quantity	10 L		
Duration	Few minutes (<5)		
Frequency	Twice a week		
Existing mitigation measures	Ventilated bench		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 0.69 ppm; Average: 0.53 ppm;	Max: 0.32 ppm	class E (≥ 0.3ppm)
TLV exceeded	**YES**	**YES**	**YES**
Causes identified for exceeding concentrations	- Poor exhaust ventilation (no chemical hood). - Very small room size (2 operators can hardly work). - Emission of formaldehyde during dilution is unavoidable.		
Proposed Risk Management Measures			
1. Provide the Unit with formalin already diluted to operational condition (buying directly from supplier).			
2. Re-arrange rooms and working spaces: functional to tasks.			
3. Provide effective exhaust chemical hood.			
4. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

Exposure Scenario no. 4

Scenario name	***Biopsies inclusion into formalin***		
Task description	Biopsies are placed into bio-cassettes and filled with formalin		
Exposure determinants			
Environment	Central lab (room A)		
Concentration	4% m/v formaldehyde solution		
Quantity	<10 mL/container		
Duration	~30 minutes		
Frequency	Daily		
Existing mitigation measures	Chemical hood		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 1.35 ppm Average: 0.49 ppm	Max: 0.23 ppm	class D (0.2-0.3 ppm)
TLV exceeded	**YES**	NO	NO
Causes identified for exceeding concentrations	- Exhaust hood is switched off too soon, just after the task is finished.		
Proposed Risk Management Measures			
1. Avoid misuses, providing task-specific training to personnel involved (i.e. leave the hood switched on for a while after the work has been done).			

Exposure Scenario no. 5

Scenario name	***Disposal***		
Task description	Residual formalin present in containers is poured into apposite sink		
Exposure determinants			
Environment	Dissection room (room B)		
Concentration	4% m/v formaldehyde solution		
Quantity	Up to several L (over 10 L very rare)		
Duration	10-15 minutes		
Frequency	Daily		
Existing mitigation measures	Ventilated bench		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 0.61 ppm Average: 0.53 ppm	Max: 0.42 ppm	class E (≥ 0.3ppm)
TLV exceeded	**YES**	**YES**	**YES**
Causes identified for exceeding concentrations	- Poor exhaust ventilation (no chemical hood). - Very small room size (2 operators can hardly work). - Containers are poured too fast.		
Proposed Risk Management Measures			
1. Re-arrange rooms and working spaces: functional to tasks.			
2. Provide effective exhaust chemical hood.			
3. Avoid misuses, providing task-specific training to personnel involved (i.e. wait few minutes between pourings)			
4. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

An Exposure Scenario for situation no. 6 at University Hospital Luigi Sacco has not been developed. The situation has not been monitored with CMS sampler and photo-acoustic monitor because the task (archiving) was not supposed to be critical, however on personnel request a Bio-check-F sampler has been activated. Formaldehyde concentrations increased if compared to results of preliminary campaign (class E vs class C), and this is probably due to the presence of unsealed containers of biological material put in a normal bin. Although archive is located in the

cellar, and operators do not stay there for a long nor they go down frequently, the removal of unsealed containers from bins is recommended, as well as the sealing of material to be kept as archive into cupboards (already present).

National Cancer Institute

Among tasks monitored (8), three of them presented formaldehyde levels clearly exceeding the TLV-C (no 2, 4 and 8). Tasks no 4 and 8 consist in the same operation, however are carried out in different environment. Further, the disposal of formalin in specimens kept in archive (in disposal room) concerns a relevant number of containers poured at same time, while the task conducted in dissection room is usually a routine task and involves fewer containers per time. Thus, three Exposure Scenarios have been developed.

Exposure Scenario no. 1

Scenario name	***Formalin upload and download***		
Task description	Formalin is uploaded, and downloaded, from processing machines. To facilitate, a funnel positioned on the tank is used during download. This operation can be performed both manually and automatically.		
Exposure determinants			
Environment	Processing room (room B)		
Concentration	4% m/v formaldehyde solution		
Quantity	20 L (2 tanks of 5 L for both upload and download)		
Duration	Less than 15 min		
Frequency	Daily (sometimes twice a day).		
Existing mitigation measures	Exhaust ventilation system: 20 air exchange per hour (theoretical).		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	-	Max: 0.54 ppm (average 0.35 ppm)	class D (0.2-0.3 ppm)*
TLV exceeded	-	**YES**	NO
Causes identified for exceeding concentrations	-Spills of formalin on the floor (usual occurrence)		
Proposed Risk Management Measures			
1. Avoid misuses, providing task-specific training to personnel involved (i.e. pay attention to potential spills during upload and download).			
2. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

*Bio-check F sampler located in the corridor in front of room B

Exposure Scenario no. 2

Scenario name	***Archives disposal***		
Task description	Residual formalin present in containers of archive is poured into apposite sink.		
Exposure determinants			
Environment	Disposal room (room C)		
Concentration	4% m/v formaldehyde solution		
Quantity	NQ[1]		
Duration	Up to 1 hour.		
Frequency	Few times per week.		
Existing mitigation measures	Chemical hood.		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 2.25 ppm Average: 1.24 ppm	Max: 2.25 ppm	class E (≥0.3 ppm)
TLV exceeded	**YES**	**YES**	**YES**
Causes identified for exceeding concentrations	-A large number of containers is emptied at the same time, in a very fast way. -Spills of formalin on the floor (usual occurrence)		
Proposed Risk Management Measures			
1. Avoid misuses, providing task-specific training to personnel involved (i.e. wait few minutes between pourings, pay attention to potential spills)			
2. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

[1]NQ: not quantifiable.

Exposure Scenario no. 3

Scenario name	***Formalin pouring***		
Task description	Residual formalin present in containers is poured into apposite sink. Containers are re-filled with new formalin		
Exposure determinants			
Environment	Dissection room (A)		
Concentration	4% m/v formaldehyde solution		
Quantity	Up to 5 L.		
Duration	Few seconds per container		
Frequency	Daily		
Existing mitigation measures	Chemical hood.		
Operator exposure			
Formaldehyde air levels	*Photo-acoustic*	*CMS*	*Bio-check F*
	Peak: 0.6 ppm Average: 0.34 ppm	Max: 0.24 ppm	-
TLV exceeded	**YES**	NO	-
Causes identified for exceeding concentrations	-Containers are poured too fast		
Proposed Risk Management Measures			
1. Avoid misuses, providing task-specific training to personnel involved (i.e. wait few minutes between pourings)			
2. Use of personal protective equipment during most critical situation (i.e. mask with AX filter).			

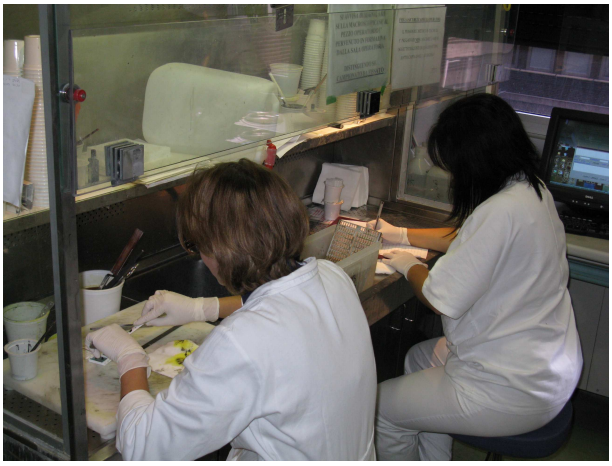
Pictures taken during monitoring at University Hospital L. Sacco:

1: Dissection of organs in dissection room (to be noted ventilated bench)

2. Archives kept in the basement

Pictures taken during monitoring at National Cancer Institute:

1. Sampling and inclusion into formalin under chemical hood in dissection room



2.Formalin download (a) and upload (b) (manual) in processing room

Discussion

4.1 European Project INDEX-UPRIC 2009

4.1.1 Levels of exposure among EU population

In the most recent surveys, the average levels of formaldehyde indoor ranged between 15 and 50 µg/m^3 (12 and 40 ppb). The maximum values were significantly lower than in the 1980s, as can be noted when comparing the various surveys carried out in Germany (GerES studies) to the most recent ones from France (OQAI, Indoor Air Quality Observatory) and AIRMEX project. The trend of decreasing concentrations can be partially attributed to the less emitting materials being developed over time in the context of various labelling schemes put in place in different European countries. Very high concentrations, in particular, have become less common. However, formaldehyde still features as one of the most common indoor air pollutants. In particular, data collected suggest that concentrations inside home are higher than those measured in offices and schools. Wood based materials, and furniture, due to their formaldehyde-resins content, are one of the main sources of formaldehyde, especially at the beginning of their employment. New buildings, dwellings furnished with many wood based materials, low ventilation, high temperatures and humidity (which facilitate the hydrolysis of formaldehyde molecules from resin's terminals), typically experience higher formaldehyde levels when compared to buildings with opposite characteristics.

Although formaldehyde is considered from scientific community a likely human carcinogen, and a major indoor air pollutant that has been acknowledged and

measured for decades across Europe, detailed and representative data on general population exposure indoors in European Union are still scarce.

In order to better understand and comment INDEX UPRIC 2009 outcomes, a brief summary of the first edition is reported.

4.1.2 INDEX 2005 summary

The first edition of EU project INDEX "*Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU*" has been funded by DG SANCO in 2004. The project objectives were the risk assessment for several pollutants representative of indoor air settings, the proposal of reference values of exposure and, recommendation of risk management measures (Kotzias et al, 2005). Substances "of concern" identified as priority (Group 1) for indoors were: formaldehyde, nitrogen dioxide, carbon monoxide, benzene, naphthalene. Formaldehyde, due to its adverse effects and its ubiquity, was deemed as the most problematic. Other chemicals were considered to be "*second* priority chemicals" (Group 2): acetaldehyde, toluene, xylenes, styrene. In Group 3: have been included "*chemicals requiring further research with regard to human exposure or dose response":* ammonia, limonene, α-pinene.

Concerning formaldehyde, a risk characterisation for general population was carried out. A NOAEL of 0.03 mg/m^3 (24 ppb) was derived based on the lowest concentration estimated not to give effects in the normal population. This evaluation, expressed by Californian OEHHA, was based on a Scandinavian work survey (Wilhelmsson and Holmstrom 1992), in which 66 workers of a chemical plant complained nasal and eye irritation, nasal obstruction, and lower airway discomfort. In the context of a risk characterisation *experiment*, the NOAEL was further divided by an assessment factor of 30, taking into account intra-species variation (10) and the consideration that children may be more sensitive than adults to formaldehyde respiratory toxicity (3). This experiment resulted in a paradoxical exposure limit of 1 µg/m^3 (0.8 ppb), which is the background concentration of formaldehyde in rural areas. Nevertheless, the exposure limit officially proposed in INDEX 2005 for formaldehyde was equivalent to the NOAEL, 30 µg/m^3 (24 ppb). Looking at exposure surveys, it emerged that almost the entire EU population was exposed at indoors

levels (median level ± sd: 26 ± 6 µg/m^3; 90th ± sd: 59 ± 7 µg/m^3; N = 6) higher than the background, with at least 20% of the European population exposed at levels exceeding 30 µg/m^3.

4.1.3 Reconsideration of formaldehyde exposure limits

After the proposal concerning formaldehyde exposure limits made by INDEX 2005 some criticism arose (Arts et al. 2008). Arts et al. from Netherlands Organisation for Applied Scientific Research (TNO) published in 2008 a review funded by the FormaCare sector group of the European Chemical Industry Council (CEFIC), assessing the risk characterisation carried out in the INDEX 2005 project. In this paper the indoor air level of 1 µg/m^3 (0.8 ppb) used in the risk characterisation exercise has been evaluated. The threshold for sensory irritation in human volunteers was identified to be 1 ppm (1,24 mg/m^3), higher than the 100 µg/m^3 (~80 ppb) indicated by WHO and considered in the INDEX 2005 project. The authors considered that nose and throat irritation, at concentrations below which hyperplasia/metaplasia occurs, are most likely the consequence of trigeminal nerve stimulation (sensory irritation). Eye irritation is recognised as the most sensitive effect reported in human volunteers, but it is considered as a merely local reaction that requires, if any, a low assessment factor. Concerning children vulnerability in relation to asthma, it is stressed the difficulty to judge the sensitivity in children because of the potential confounding factors in the evaluated studies. It is concluded that an indoor air level of 120 µg/m^3 (~0.1 ppm) can be considered safe and appropriate for the general population, as indicated by Appel et al. in 2006.

The INDEX UPRIC 2009 project, adopted a different, up-to-date approach in assessing formaldehyde hazards for human health and in indoor exposure limit calculation, basing its assumptions on the most recent scientific data, choosing objective, clear, toxicological endpoints from studies conducted in controlled conditions of exposure and applying chemical specific uncertainty factors as described in chapter Materials and Methods.

4.1.4 Protection from effects other than irritation

Several considerations have been elaborated to explain and support the reference value calculated.

The range of concentration proposed in INDEX UPRIC 2009 (70-100 ppb or 90-120 µg/m^3), is considered protective also from impairment of pulmonary function. Human studies investigating asthma and hyper-sensitisation due to formaldehyde exposure are not entirely consistent among each other and there is no clear and unambiguous evidence that children may be more sensitive to formaldehyde toxicity than adults. However, a possible mechanism explaining the association of the formaldehyde exposure with asthma exacerbation has been recently hypothesised (OEHHA, 2008). There is also some concern about synergistic effects between formaldehyde and allergens that may favourite asthma exacerbation (Casset et al., 2006).

The threshold for pulmonary effects is above 1 ppm, as most studies investigating this endpoint report a LOAEL between 2 and 3 ppm (Paustenbach et al. 1997). A potential uncertainty factor for children and asthmatic subjects vulnerability should be applied to these threshold values, and not to NOELs for sensory irritation. In the hypothesis of applying a default uncertainty factor of 10 to the threshold for pulmonary effects, the reference value obtained would be in the order of 0.1 ppm, which is in the same range of the one based on sensory irritation.

Toxicological data from long-term studies seem to show that irritating effects are concentration rather than dose (i.e, concentration per time) depended. Paustenbach 1997, OEHHA 2008 and others reviewed several chronic and sub-chronic studies on animals (Rush et al 1983, Wilmer et al 1989, Woutersen et al 1989), which suggest the concentration-dependent nature of irritation and cytotoxicity due to formaldehyde exposure. Particularly, OEHHA deems that NOAELs and LOAELs are similar in the reviewed studies regardless of exposure duration, and did not apply any ‘sub-chronic uncertainty factor’ in the calculation of chronic Reference Exposure Limits (RELs). Also pulmonary functionality was reported to be not affected in sub-chronic exposure to formaldehyde concentrations below 2 ppm.

Nevertheless, further toxicological data related to exposure to long-term, low average, levels of formaldehyde, are required to exclude any life-long cumulative effect.

Concerning carcinogenicity, the most accredited hypothesis is that inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation within the respiratory tract does represent a carcinogenic hazard (Liteplo and Meek, 2003). The carcinogenic process may be explained as the result of cytotoxic damage following severe tissue irritation (Arts, Rennen and de Heer 2006). Therefore, preventing irritation should be sufficient in order to protect from the potential carcinogenic effect in upper airways, which is generally observed in animals starting from long-term exposure to 6 ppm (Kerns et al 1983, Monticello et al. 1996). However, outcomes of in vivo genotoxicity studies (currently inconclusive) will have to be considered, particularly in relation to a potential association of formaldehyde with other tumours than those located in the site of exposure (airways tissues), such as lympho-hematopoietic tumours.

Since the reference concentration range here calculated, 70-100 ppb or 90-120 µg/m^3 for short term exposure is, at least, one order of magnitude lower than the threshold level observed for cytotoxic damage in the nasal mucosa (Arts, et al. 2006, WHO 2000), the general population exposed to these concentrations can be considered to be protected also against the risk for nasal-pharyngeal cancer. Outcomes from studies about genotoxic effects are currently not entirely consistent, but should be evaluated and taken into account in the assessment of formaldehyde carcinogenic potential, considering also other tumours sites than nasopharyngeal cancers, such as lymphohematopoietic system. In addition, biologically-motivated computational modelling can be a useful tool in evaluating cancer risk for human respiratory tract (Conolly et al 2003 and 2004). Relevant outcomes on this topic published so far have been reported in table B of Appendix D.

4.1.5 Comparison with other reference values

Although selected studies for endpoint identification and the method of calculation are different, the exposure reference range proposed by INDEX UPRIC 2009 is in the same order of magnitude of several short-term exposure limits for indoor environment recommended by several organisation. These guideline values, which have been published in last years, i.e. by HEALTH CANADA (2005), AFSSET - France (2007), RIVM – The Netherlands (2007) and by OEHHA - US (2008), are reported in table

4.1.3.1. Further, in Appendix D most of the formaldehyde evaluations by international or national institutions are reported and discussed.

Table 4.1.3.1. Proposed formaldehyde air quality guidelines (indoor/outdoor) by several national/international organisations

FORMALDEHYDE AIR QUALITY GUIDELINES ($\mu g/m^3$)			
	Short-term exposure	**8-hour average**	**Long-term exposure**
WHO (2000): Air quality guidelines.	100 (1) (30-minute average)	-	-
HEALTH CANADA (2005): Proposed residential indoor air quality guidelines for formaldehyde.	123 (2) (1-hour average)	50 (2)	-
AFSSET (2007): French indoor air quality guidelines.	50 (3) (2-hour average)	-	10
RIVM (2007): Health-based guideline values for indoor environment	120 (30-minute average)	-	1.2(4) 10 –annual average(5)
OEHHA (2008)	55	9	9

(1) "Exposure level at which there is a negligible risk of upper respiratory tract cancer in humans".
(2) "The cancer risk associated with a lifelong exposure to that concentration of formaldehyde is estimated to be negligible".
(3) "Also protecting against other suspected effects, such as respiratory function impairment".
(4) Adopted by RIVM in 1995
(5) MPR Adopted by VROM (Ministry of Housing, Spatial Planning and the Environment)

4.1.6 The relevance of exposure characterisation

As shown in recent surveys, formaldehyde remains one of the most common indoor air pollutant. Particular attention must be paid to the exposure assessment which is a

requisite for risk assessment and management purposes. The association of possible health effects encountered in exposed population with environmental levels especially, should be analysed with awareness, looking at concentration fluctuations and at the monitoring method adopted. Among available exposure data reported in indoor air surveys, results are often not adequate to perform a risk characterisation. Reasons can be identified in several aspects, being probably the most important the fact that, very often, concentrations are reported as TWA of several hours or even days; neither average concentrations are representative of real levels of exposure nor a specific health endpoint can be correctly associated to TWA. Further, in many surveys exposure determinants are not identified and/or exposure scenarios are not thoroughly understood.

However, in some studies reported here, concentrations above 100 µg/m^3 have been observed and can be expected to occur quite often during some domestic tasks or soon after home refurbishment, especially in the absence of proper ventilation. Other common practices resulting in secondary sources of formaldehyde indoors, may even worsen the scenario of short-term/acute exposure to formaldehyde. For example, the more and more widespread use of fragrances or air fresheners can result, in presence of ozone (even at very low concentrations), in formaldehyde and ultra-fine particulate matters production (ECA-IAQ, 2007). Environmental Tobacco Smoke too is considered a relevant source of formaldehyde in domestic setting as well as the use of antibacterial detergents.

The matter is that such situations that are potentially leading to peak concentrations can hardly be detected with conventional, in particular passive, air monitoring techniques and without a deep understanding of exposure scenarios.

In the light of above considerations, health effects reported in community surveys should not be associated with time-weighted average levels, which are usually reported when using traditional air monitoring techniques (either active or passive). If possible, eventual adverse effect shall be related to concentrations exceeding a certain threshold. Most of the air monitoring campaigns carried out until now are not detailed enough to fully characterise the exposure and, hence, to perform a correct risk evaluation. The identification of crucial situations leading to formaldehyde exposure as well as of all the parameters determining its emission, spatial distribution and air concentration can improve the scenario depiction. Moreover, the adoption of

in-continuous gas detectors, capable to identify and monitor emissions in real-time i.e. during critical circumstances, can easily detect exceeding air levels.

4.1.7 Recommendations

The exposure reference value for formaldehyde is suggested to be 70-100 ppm or 90-120 μg/m^3 as short-term exposure (30 minutes). In order to reduce and contain formaldehyde exposure the following actions are recommended to policy makers:

- Minimise the emissions of formaldehyde from building materials, products and furnishings (i.e. through the application of certification systems);
- Discourage the use of formaldehyde in household/office products;
- Require product labelling providing information on potential formaldehyde release from household and building products;
- Ensure health based ventilation for indoor environments;
- Raise public awareness and provide information to the public about the sources and prevention of risks from exposure to formaldehyde in indoor environments.

Long-term implications

Toxicological data associated with long-term exposure to formaldehyde are currently not exhaustive to define a long-term exposure level to exclude life-long health hazards. In any case, in order to meet the short-term reference range proposed, long-term average exposure levels (i.e. those detected with passive air monitoring) will need to be kept *significantly lower*, in order to take into account exposure fluctuations and short–term releases of formaldehyde.

4.2 Exposure characterisation and Exposure Scenarios in hospitals

4.2.1 Occupational exposure to formaldehyde in Pathology laboratories.

Occupational exposure to formaldehyde presents marked differences if compared with indoor exposure, especially for what concern laboratory settings. Personnel working in Pathology units (technicians, anatomists, pathologists, researchers, students and attendants) are exposed, even if to very different extents, to concentrations generated by their working activity, during various tasks which involve the use (or the presence) of formalin. Formaldehyde contained in the solution easily evaporates and produces peaks of concentration in the close vicinity. Those peaks can even reach ppm levels posing a non-negligible risk for personnel health.

In table 4.2.1.1 some studies published in the last 10 years investigating occupational exposure to formaldehyde in Pathology labs are reported. Using either passive or active sampling techniques , both environmental and personal monitorings show that formaldehyde levels can reach worrying concentration (see in particular Orsiere et al, 2006, and Costa et al, 2008).

Table 4.2.1.1 Levels of formaldehyde exposure in Pathology laboratories reported during the last decade.

Study	Sampling method reported	Exposure level
Costa et al, 2008	Personal sampling 8 hrs TWA	0.04÷1.6 ppm
	Environmental sampling 8 hrs TWA	-macroscopic examination: 1.50 ppm; -disposal: 4.4 ppm.
Pala et al, 2008	Personal passive sampling 8 hrs TWA (among different hospital units, including pathology).	3.5÷216.1 ppb

Study	Sampling method reported	Exposure level
Orsiere et al, 2006	Active sampling 15 min	<0.1÷20.4 ppm.
	Passive sampling 8 hrs TWA	<0.1÷0.7 ppm
Ohmichi et al, 2006	Environmental sampling (4-6 hrs)	0.23÷1.03 ppm.
	Personal sampling (1.1-6 hrs)	0.80, 0.45 and 0.51 ppm (instructors) 1.02, 1.08 and 0.89 ppm (students).
Burgaz et al, 2002	Active monitoring in the breathing zone (sampling time not reported)	2÷4 ppm
Shaham et al, 2002	Personal and environmental sampling (15 min).	0.04÷0.7 ppm (laboratory assistants and technicians).
		0.72÷5.6 ppm (physicians and hospital orderlies).

Air sampling methods reported in literature are often not described in detail. Being detected with an in-continuous (photo-acoustic gas monitor) or with an active, short-time, technique (maximum 10 minutes measurement, CMS sampler), maximum levels of formaldehyde measured in our study seem, to be generally lower than many of those reported in table 4.2.1.1

4.2.2 Comparison of exposure data with the TLV-C

Threshold Limit Values (TLVs) are set by American Conference of Industrial Hygienists (ACGIH) to be protective of both acute and long term adverse effects on workers professionally exposed to a certain substance. The comparison of the TLV to concentration values measured with the three techniques in both hospitals is necessary to identify situations leading to potentially critical exposure for operators'

health. For formaldehyde the TLV is set at 0.3 ppm as *ceiling* value (TLV-C) indicating that *this exposure limit should not be exceeded at any time.* In consideration of this*, v*alues to be compared with the threshold limit should be measured within the shortest time period to be representative of real levels exposure. In fact, in the case of exposure to formaldehyde in occupational settings, the sampling time is a crucial issue, as due to the nature of the substance, fluctuations of air concentration might occur suddenly. Photo-acoustic monitor, giving a measurement every ~90 seconds appears to be the most suitable method for the purpose. Hence, a primary importance is given to photo-acoustic monitor results in representing actual levels of exposure in respect to those of the other two monitoring techniques.

As reported in chapter Results, CMS and Bio-check F samplers present discrepancies when compared to photo-acoustic, but also between each other, principally due to different sampling times. Both CMS and Bio-check-F samplers cannot give a *real-time* reading of air concentrations, thus concentration values measured in 5-10 minutes or 2 hours respectively, have to be compared with caution to a threshold limit.

In this study, to consider the exposure during a task as critical and therefore, to implement an Exposure Scenario, it has been sufficient that results of photo-acoustic monitor clearly exceeded the TLV-C even if the other two did not. In the case of invalidated photo-acoustic measurements, CMS and Bio-check F samplers have been carefully evaluated and used for the comparison with the TLV-C.

University Hospital L. Sacco

Among formaldehyde levels found at University Hospital L. Sacco, 76% of the photo-acoustic measurements (n=140) exceeded the TLV-C. In particular, 98%, 31%, 78% of the concentrations determined by the photo-acoustic monitor were higher than the TLV-C during dissection in room B (situation no. 1), various tasks in room A (situation no. 2), and during biopsies inclusion into formalin in room A (situation no. 4), respectively. Further, in these three situations formaldehyde levels exceeded 1 ppm for several minutes, indicating a characteristic “peak pattern” of exposure. Although all tasks grouped in situation no.2, were not identified as critical, as they do not involve the direct use of formalin, levels of formaldehyde measured reached a peak of 1.05 ppm. Such a concentration is not attributable to routine tasks carried out

during the measurement (i.e. specimens processing, colouration, microtome, sorting) and sources have to be searched somewhere else. During formalin dilution and disposal in room B (situation no. 3 and 5) maximum level detected with photo-acoustic method are somewhat lower, being 0.69 ppm and 0.61, respectively. However, 100% of photo-acoustic measures are above the TLV-C in both situations.

Concentrations measured by CMS sampler, although did not recognise peak levels, exceeded the TLV-C during situations 3 and 5 (maximum levels 0.32 and 0.42 ppm, respectively). This may reflect less fluctuating concentration patterns if compared with no. 1, 2 and 4, where data measured by CMS sampler resulted to be below the threshold limit. Also Bio-check F sampler reached the highest concentration class (≥0.3 ppm) in situation no. 3 and 5 (being 2 hours the measurement time, in the same environment, it has been used one sampler) but not in situations no. 2 and 4. Surprisingly, CMS sampler detected levels lower than the TLV-C during situation no. 1 but did not Bio-check F (see summary in table 4.2.2.1). Bio-check F sampler reached the highest concentration class in situation no. 6 also, in room C (archive), also not expected to be critical when specimens are kept in sealed containers (the result of the preliminary monitoring was 0.1-0.2 ppm).

Table 4.2.2.1 Summary data of University Hospital L. Sacco: concentrations exceeding ACGIH TLV-C for formaldehyde

Task/situation	Environment	Photo-acoustic % > TLV	CMS > TLV	Bio-check F class ≥ TLV
No. 1	Room B	98	No	Yes
No. 2	Room A	31	No	No
No. 3	Room B	100	Yes (1/1)	Yes
No. 4	Room A	78	No	No
No. 5	Room B	100	Yes (2/2)	Yes
No. 6	Room C	-	-	Yes
No. 7	Room Z	0 (<LOD)	-	No

National Cancer Institute

Among formaldehyde levels found at National Cancer Institute, 32% of valid photo-acoustic measurements (n=98) exceeded the TLV-C. A marked peak of concentration is found during disposal (pouring residual formalin, situation no. 4)

carried out in room C, where formaldehyde levels reached 2.25 ppm. The peak has the TLV-C) and CMS sampler. This may mean that concentrations above 2 ppm occurred for at least 5 minutes (minimum sampling time of CMS sampler). In the same situation, Bio-check F sampler resulted in class E in both environmental and personal monitoring.

In situation no. 2, 6 and 7, photo-acoustic monitor results had to be discarded, as they have been invalidated due to the presence in the same environment (processing room) of ethanol and xylenes, which give positive interferences, while CMS sampler exceeded the TLV-C in situation no. 2 only (during formalin download and upload). Bio-check F sampler resulted equal or higher than the threshold limit in situation no. 6 only (biopsies positioning in bio-cassettes). During formalin download and upload Bio-check F sample no. 8 had a void result. Thus, it has been considered Bio-check F sample no. 9 located in corridor B, just in front of the processing room (door left open, distance from operation < 2 m), as a surrogate for situation no. 2: it resulted in class D (0.2-0.3 ppm).

During specimen dissection 1 (biopsies) and 2 (organs) (situations no. 1 and 3) photo-acoustic monitor results exceeded the TLV-C just once (concentration measured: 0.35 ppm) during biopsies sampling (see table 4.2.2.2.). However it has not been considered relevant enough to identify the task as critical and to develop an Exposure Scenario. CMS measurements seem to be in good accordance with photo-acoustic monitor results in these situations, being the maximum levels detected not higher than the TLV-C. On the opposite, Bio-check F resulted in class E (≥ 0.3 ppm) in both situations, being aware that during situation no. 3 it has been pinned on the breast pocket of a technician (personal monitoring).

Due to the strict schedule of the personnel involved, situation n. 5 (washing of recyclable containers in ex autopsy room) and 8 (pouring residual formalin in dissection room) have been monitored with 2 techniques only, CMS and Bio-check F samplers in the first case and, photo-acoustic monitor and CMS sampler in the second. Results were below the TLV-C with the exception of those obtained with photo-acoustic method during formalin pouring, whose measurements exceeded the TLV-C once (20%, 1 of 5 measurements). Even if conducted under chemical hood this task may lead to high level of exposure, thus it has been considered as critical, and an apposite Exposure Scenario has been developed (see the disposal of residual formalin from archive specimens, situation no. 4)

Personal monitoring conducted with Bio-check F samplers revealed a non-negligible condition of exposure of technicians, since the 3 valid samples resulted in the highest concentration class (equal or above the TLV-C). Working procedures adopted by operators during these and other situations have been observed during monitoring and are discussed in paragraph 4.2.3.

All the other Bio-check F samplers used for screening purposes in many environments (see table 3.2.4.1 in chapter Results), have been useful to check levels of formaldehyde where fluctuations are not expected, as i.e. in offices, corridors or single laboratories where there is not a direct use of formalin. Only sample no. 9, located in corridor B in front of processing room during formalin download/upload (door left open), resulted in class D (0.2-0.3 ppm), while in all other environments concentration class detected is much lower (A or B).

Table 4.2.2.2 Summary data of National Cancer Institute: concentrations exceeding ACGIH TLV-C for formaldehyde

Task/situation	**Environment**	**Photo-acoustic % > TLV**	**CMS > TLV**	**Bio-check F class ≥ TLV**
No. 1	Room A	4	No (<LOD)	Yes
No. 2	Room B	Dis[1]	Yes (6/7)	No
No. 3	Room A	0	No	Yes (operator)
No. 4	Room C	100	Yes (3/7)	Yes
No. 5	Room D	-	No	No
No. 6	Room B	Dis[1]	No	Yes
No. 7	Room B	Dis[1]	No	No
No. 8	Room A	20	No	-

[1]Dis: discarded because of positive interferences.

Sometimes, Bio-check F sampler measured not expected, “paradoxical”, formaldehyde concentrations if compared to photo-acoustic and CMS measurements in the same situation (namely, Bio-check F results higher than the other two, as in situation no 1 at National Cancer Institute). This may be explained by the fact that its sampling time has a fixed duration of 2 hours, in which it must be left in the same room. The other two techniques for organisation and schedule of the monitoring survey, are generally left to monitor the same task for one hour at maximum. After

that photo-acoustic monitor and CMS sampler have been removed, working conditions may have varied or an unnoticed circumstance have occurred.

4.2.3 Considerations on proposed RMMs

The two hospitals, being focused on different medical specialities, do present very different work organisation, logistic and mitigation measures already put into place. However, both present critical situations, potentially leading to a risk for operators' health. A number of these situations can be resolved (at least partially) by paying attention on working procedures, especially avoiding misuses. To do this, personal training is a requisite. They must not only be informed on how to correctly perform a certain task, avoiding risky situations, but they must be aware of the intrinsic characteristics of formaldehyde such as physical-chemical behaviour (i.e. being a gas, it naturally tends to leave the solution) and toxicological properties.

To summarise, Risk Management Measures proposed in the two hospital concern interventions to be implemented at different levels:

- *logistics*: re-arranging room and spaces in function to tasks;
- *organisation*: buying ready-to-use formalin, already diluted to operational dilution, as well as ready-to-use containers (already filled with formalin);
- *mitigation*: providing effective ventilation (chemical hood or exhaust ventilation)
- *personal protective equipment*: providing masks (i.e. AX filters) and also goggles
- *training*: general indications to all staff of Pathology Units and specific to operator for critical tasks. Motivating personnel to use personal protective equipment is necessary.

4.2.4 Considerations on monitoring techniques

Air sampling methods adopted in this study have been evaluated on the basis of the output data and their accordance (see also PCA analysis outcomes in Appendix C). Advantages and disadvantages arose for each technique can be summarised as follows.

Bio-check F disposable sampler (passive technique)	
Advantages: + Easy to use; + Cheap; + Can be used for both environmental and personal sampling (pinned on any garment); + No maintenance needed; + Suitable for preliminary surveys or quick, undemanding controls; + Useful in environments not interested by the direct use of formalin (i.e. corridors, archives, offices), where relevant fluctuations in formaldehyde levels are not expected.	Disadvantages: – Cannot recognise any fluctuations (giving a 2 hours TWA); – Not precise measuring (semi-quantitative reading); – Colour reading can be subjective; – Limited range of measurement for occupational purposed (max. ≥ 0.3 ppm).

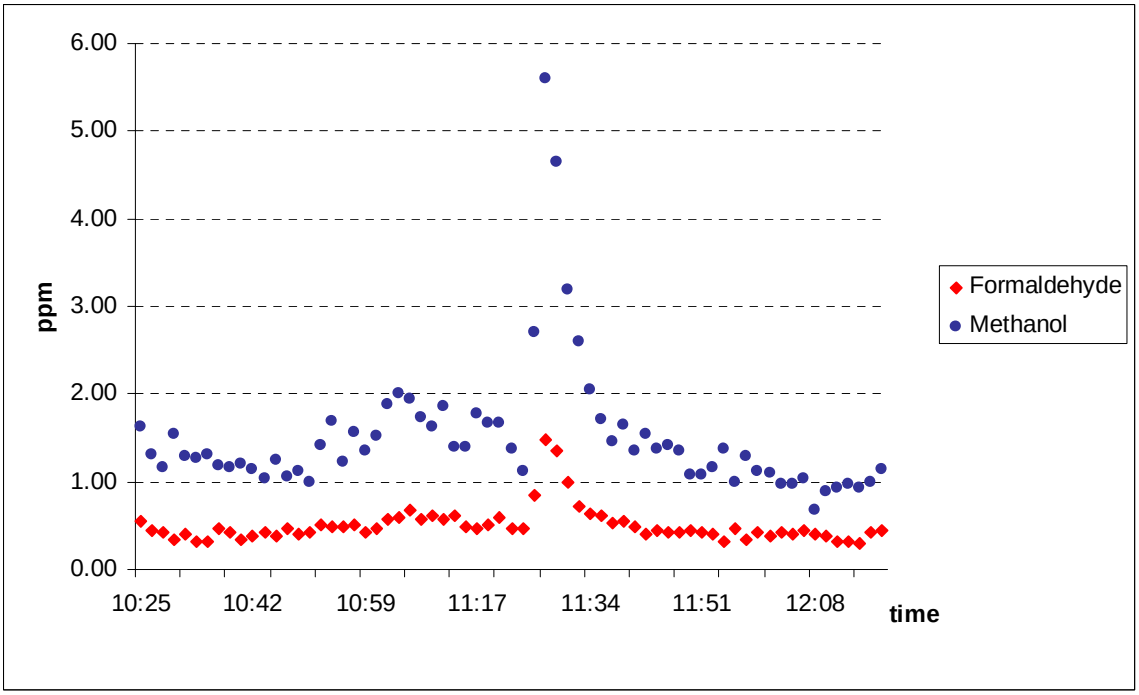
CMS sampler (active technique)	
Advantages: + Easy to use and move; + Quite cheap (if ordering many chips); + Quick reading on monitor; + Can be used for both environmental and personal sampling (strap provided); + No particular maintenance needed; + Can be used with different chips to monitor numerous other gases; + Measurement range suitable for occupational purposes (0.2-5 ppm)	Disadvantages: – Difficulties in blank reading (due to chip calibration); – Manual activation; – Not effective to detect peak concentrations (tend to underestimate); – Reproducibility is not high: reported on label ± 30% ; this is confirmed on field; – Feels temperature and humidity effects (appears less reliable during summer season)

Photo-acoustic gas monitor (in-continuous technique)	
Advantages: + Once switched on it gives approximately real-time measuring (one measure every~90 s) + Quick reading on monitor; + **Effective to detect peak concentrations and fluctuations;** + Measurement of other gases at the same time with apposite filters (i.e. methanol, CO_2, etc..); + Measurement range suitable for occupational purposes (0.04 -10 ppm).	Disadvantages: – Specificity: other gases can easily give interferences if specific filters are not assembled; – Expensive; – Need maintenance; – Cannot be used for personal sampling.

In the light of above considerations, it seems that photo-acoustic gas monitor would be the most suitable and fit-to-purpose method to thoroughly understand formaldehyde air levels in occupational settings where high concentration fluctuations occur, such as Pathology laboratories. Nevertheless, many aspects have to be taken into account, starting from economic resources, but also the purposes of the survey. Of course, when characterising exposure in order to perform a risk assessment, or when associating formaldehyde levels with specific health effects encountered in exposed operators, an in-continuous technique is recommended. However, if a photo-acoustic gas monitor is chosen, particular attention must be paid to the aspect of interferences. Unfortunately, while sensitivity is very high (LOD is 0.04 ppm), specificity can be low if filters for those gases likely to interfere are not assembled on the device. In particular, when monitoring formaldehyde, possible (positively) interfering substances consist in alcohols and other low-weight aldehydes. A filter for methanol is assembled on the device used in this study and, when activated, it measures its air concentration at the same time of formaldehyde. This is very useful, since when measuring formaldehyde released from formalin buffered with methanol, as in the case of University Hospital L. Sacco, it can work as a control. If formaldehyde fluctuation has the same trend of methanol (see chart 4.2.4.1), it can be reasonably assumed that concentrations measured are due to the release from formalin, thus are not compromised by the presence of interferences. While monitoring at National Cancer Institute, instead, the possible presence of alcohols such as ethanol and xylenes in processing room has been promptly reported by operators. Photo-acoustic measures resulted clearly affected by positive interference

attributable to these gases, having formaldehyde concentration shown on the monitor raised up to the unrealistic level of 18 ppm. Further, as in this hospital, formalin solution used is buffered with phosphates rather than methanol, no control method can be applied. This is the reason why all the measurements conducted with photo-acoustic monitor in processing room have been discarded.

Chart 4.2.4.1 Formaldehyde vs methanol fluctuations during specimens dissection at University Hospital L. Sacco.



In conclusion, a careful evaluation of the situation to be monitored is a requisite, as well as a consideration of the survey objectives, in order to adopt the most suitable method without wasting resources. For preliminary screenings, and undemanding checks, both passive (especially for those area where peaks are not expected) and active techniques such as Bio-check F and CMS samplers can be reasonable solutions, bearing in mind their most critical intrinsic limit, the missing depiction of peak concentrations.

Conclusions

5.1 European Project INDEX-UPRIC 2009

In 2009, DG SANCO funded an update of the 2005 project INDEX "*Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU*". DG SANCO required a particular focus on formaldehyde, on the basis of new papers published following its re-classification in Group 1 (sufficient epidemiological and scientific evidence for an association with nasopharyngeal cancer) by IARC. INDEX-UPRIC 2009 ("*UPdate of PRIority Compounds"*) aimed at reviewing recent scientific data, but also at re-examining previous studies and re-considering the reference values proposed in 2005. From selected results of scientific literature and an innovative approach in applying uncertainty factors, making the best use of chemical specific data on toxicodynamics and toxicokinetics, new reference limits have been proposed for exposure to formaldehyde in indoor settings.

The reference range of values for short-term exposure (30 minutes) proposed at EU level is 70-100 ppb (or 90-120 µg/m^3); it is comparable to most of exposure limits set by other national or international organisation. WHO in particular, in the latest version of IAQ guidelines (just published in December 2010), even if resulting from a different calculation, recommends a limit of 100 µg/m^3 (~80 ppb) for short-term exposure.

The reference values proposed by INDEX UPRIC 2009 should be used for the risk characterisation of situations related to acute exposure to formaldehyde indoors. In the light of scientific data available, it can be considered protective from carcinogenic effects in relation to short-term exposure, although it is derived from an irritation endpoint. Always looking at the scientific evidence available so far, there is no indication of cumulative effects following exposure to low concentrations (below 1 ppm), as adverse effects seem

to recover shortly after exposure period. Current knowledge allows to reasonably assume that the proposed reference range of concentrations is also protective from long-term health effects due to repetitive short-term exposures. However, attention must be paid at the outcomes of genotoxicity studies (currently inconclusive), particularly with concern to a potential association of formaldehyde with increased incidence of tumours other than those located in the site of exposure (airways tissues).

5.2 Exposure characterisation and Exposure Scenarios in hospitals

The hazard characterisation of formaldehyde carried out in INDEX UPRIC project indicates that recurrent, short-term, peak exposures, rather than exposure to constant levels, are expected to adversely affect eyes and upper airways in exposed subjects, posing also a potential risk for more severe health outcomes. Exposure to formaldehyde in occupational settings, and particularly in Pathology labs, appears to be characterised by concentration fluctuations and peaks. To perform a correct exposure assessment in Pathology Units, and to eventually associate exposure levels with health effects, an in-depth understanding of determinant factors of exposure and actual air levels, is a requirement. The project aimed to reach this goal through the development of detailed Exposure Scenarios and the characterisation of concentration fluctuations during specific tasks in Pathology Units of two different hospitals.

Three monitoring methods have been adopted: passive, active and in-continuous techniques have been tested and their outcomes analysed. Potential hazards for operators' health have been identified during the performance of several tasks, being measured formaldehyde levels clearly above the TLV-C set by US ACGIH (0.3 ppm). From circumstances observed during monitoring, some misuses have been identified as well as inappropriateness of some organisational, logistic, and mitigation factors leading to high level of exposure (even above 1 ppm). Exposure Scenarios for critical tasks have been presented, including operational conditions, formaldehyde levels detected by the three techniques, possible causes of rises above the TLV-C, and proposed RMMs .

Due to intrinsic properties of formaldehyde, its release from formalin solution is unavoidable, thus the implementation of RMMs is particularly crucial to avoid excessive exposure of operators. Much can be done in order to reduce critical situations, but

measures to put into practice must be shared within all personnel working in the Unit. Less problematic alternatives (i.e. glutaraldehyde) should be also taken into account, considering the current debate on carcinogenicity and being formaldehyde in revision of classification at EU level as a consequence of a French request to place it among *Carcinogens Category 1*.

Proposed RMMs have started to be put into place by Prevention and Protection Service of both hospitals. Very soon after their implementation another monitoring survey is foreseen, in order to check their effectiveness and appropriateness.

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Appendix A

Exposure modelling exercise

Before starting with monitoring campaigns, exposure estimation has been carried out utilising the software ConsExpo 4.1. The programme, developed by Dutch Institute for Public Health and Environment (RIVM) is freely downloadable on the institute website. It was created to estimate exposure to chemical substances released by consumers' products, nevertheless having a free-input data mask, it has been considered for a preliminary estimate of exposure to formaldehyde in occupational settings such as laboratories. Input data of a typical laboratory of Pathology Unit at University Hospital Luigi Sacco have been put in the model for the inhalation route, as shown in figure A.1. In particular, the "*exposure to vapour model*" has been chosen, which describes a scenario in which a compound evaporates from a surface into the room air, for example, spread onto a bench or from a can of product. The compound may contain 100% of the product, or be part of a mixture or dilution (as in the case of formalin). The concentration in the room air will depend on the amount of chemical present in the room, the room size, ventilation of the room air, vapour pressure of the compound and the rate at which the compound is released into the air (input data, see figure A.1).

Depending on the information available on physicochemical properties of the compound and the use of the product, different modes of release of the compound from the product can be selected to calculate the release of the compound into the room air.

The Scenario hypothesis chosen among those proposed for exposure to vapour model is "*constant rate release*", a second tier scenario. It describes the release of a compound with a constant rate over a certain period of time. During this time, the compound is simultaneously removed from the air by ventilation of the room.

The air concentration of the compound at time *t* is calculated as follows:

$$C_{air} = \frac{A_0 \times w_f / t_r}{qV} \times \left(1 - e^{-qt}\right)$$ when t<tr

and

$$C_{air} = \frac{A_0 \times w_f / t_r}{qV} \times \left(1 - e^{-qt_r}\right) \times \left(1 - e^{-q(t-t_r)}\right)$$ when t>tr

where:

Cair: concentration of compound in the room air [g/m3]

tr: release time [s]

Ao: amount of product used [g]

wf: weight fraction of the compound in the product [fraction]

V: room volume [m^3]

q: ventilation rate of the room (number of air changes per time) [1/s]

Hypothesised input data for the Pathology lab:

A_0= 10 (g)

tr = 30 (min)

wf = 0.04

V = 80 m^3

Input data inserted try to simulate a plausible routine task which could be pouring a certain amount of formalin from a container in dissection room. This operation could be repeated for several times per day. Results of the exposure estimation have been then compared with level of formaldehyde measured in laboratories, in particular with those found in dissection room of University Hospital L. Sacco. Peak values obtained from the model are in the same order of magnitude.

Figure A.1 ConsExpo 4.1: input mask for the inhalation model “exposure to vapour” at constant release rate adapted to formaldehyde exposure in a pathology lab-

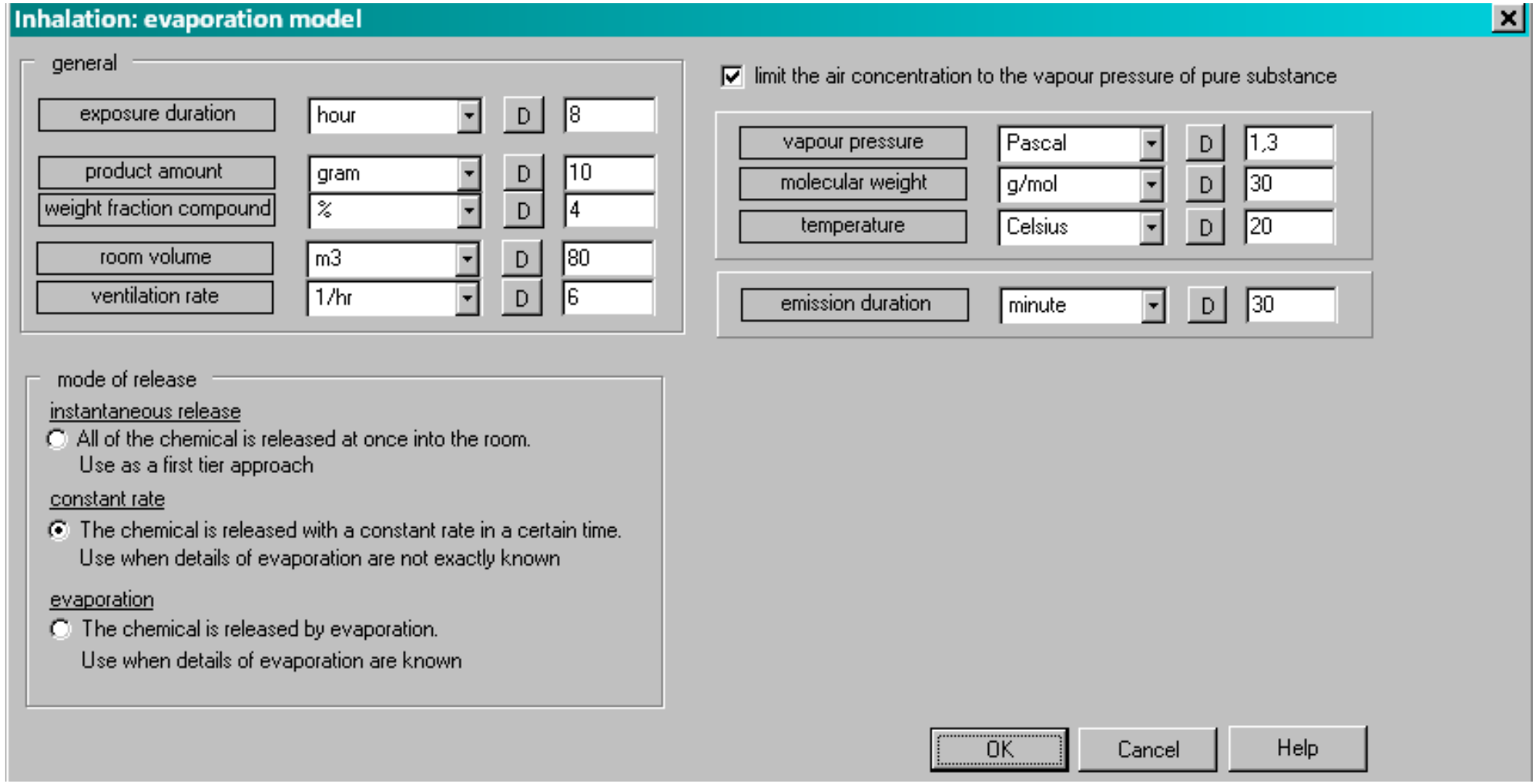
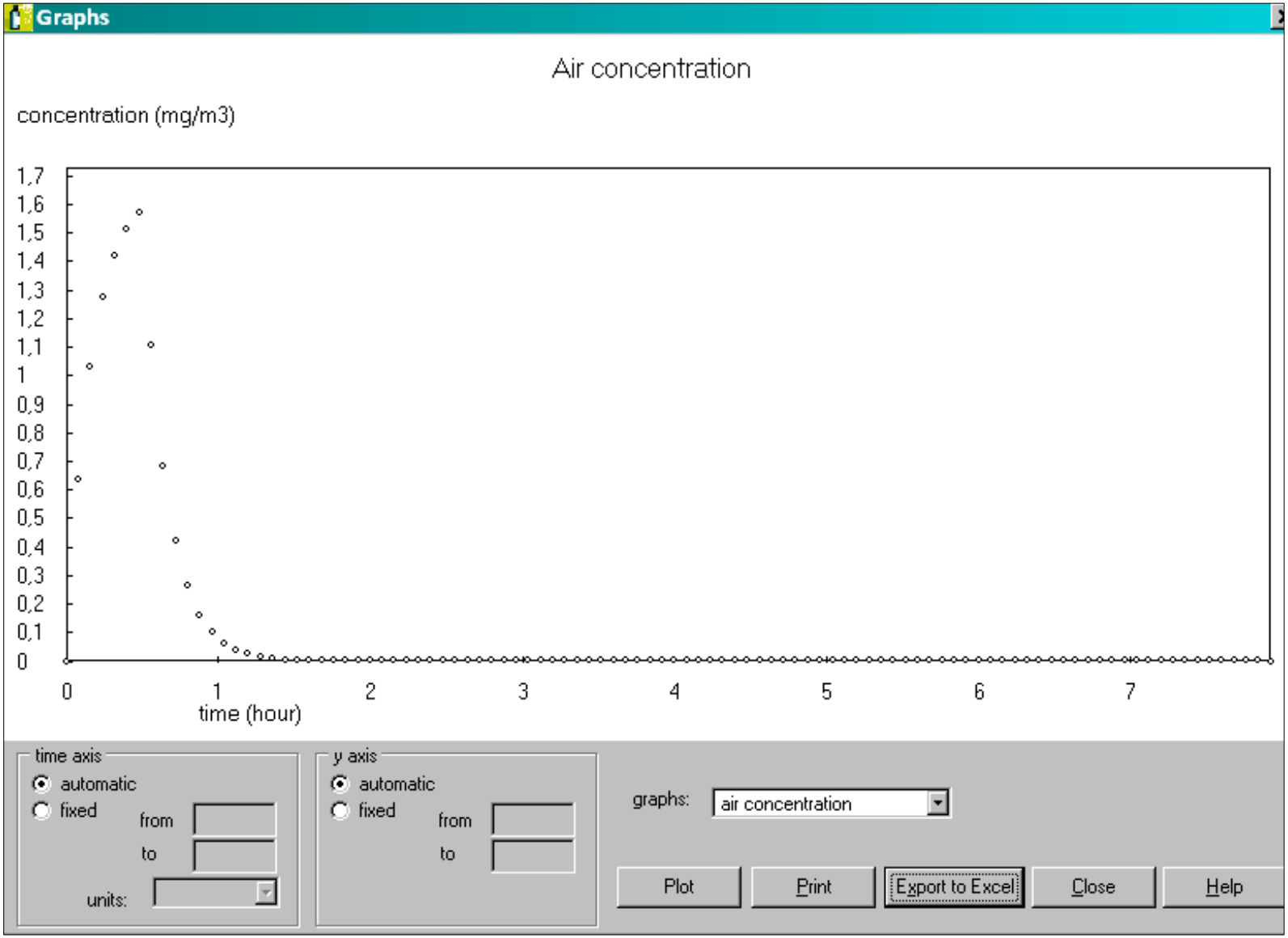


Figure A.2 Plotted output data



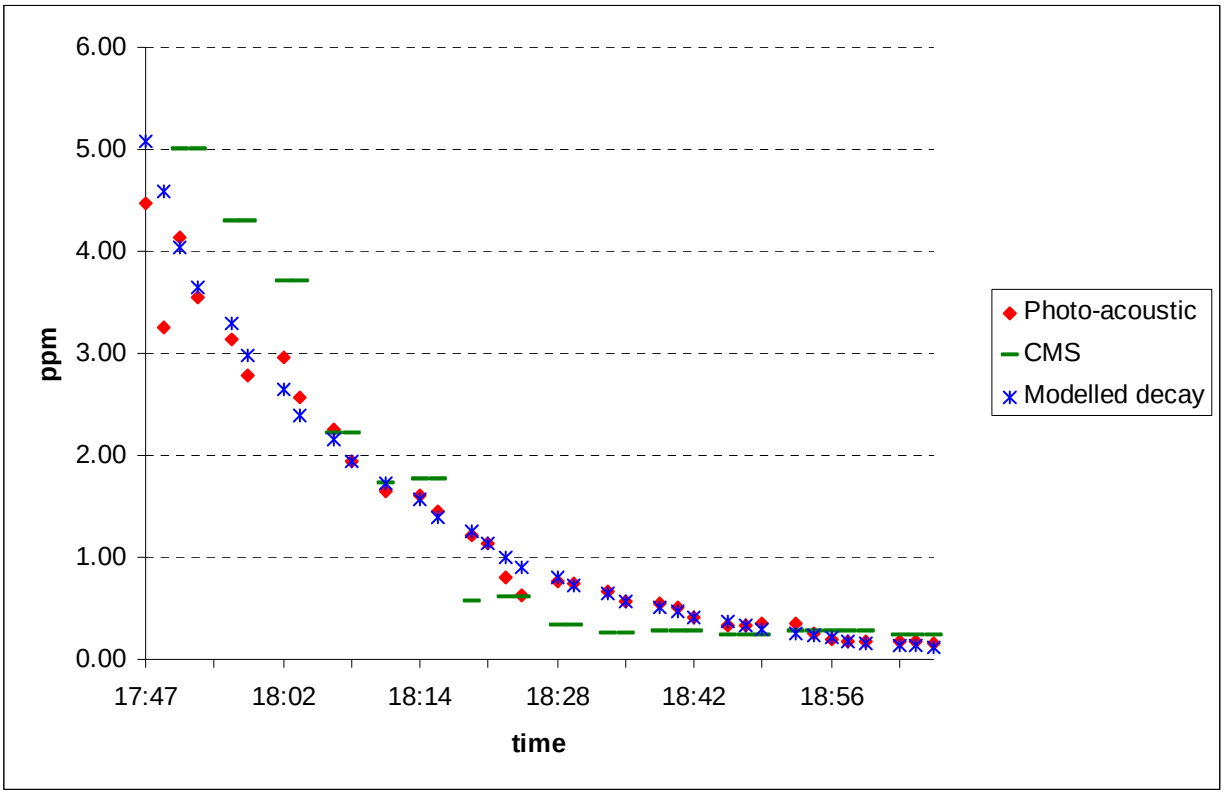
Appendix B

Results of pilot test

The methodology followed during pilot test is described in chapter Materials and Methods, paragraph 2.2.3.

In chart B.1 concentration values measured by photo-acoustic monitor and CMS sampler during the decay phase vs dilution model (Clausen et al, 1993) are depicted.

Chart B.1 Decay of formaldehyde concentrations measured by two methods vs dilution model.



Appendix C

Results of PCA

Data obtained from the monitoring at University Hospital L. Sacco have been used to perform a PCA. In total, 153 points in time have been measured at Pathology Unit. Sixty-one have been excluded from the PCA since measurements were not paired. Tables C.1 and C.2 illustrate summary statistics.

Table C.1. Mean, standard deviation and range of the paired measurements

Variable	Observations	Minimum	Maximum	Average	Standard deviation
Photo-acoustic	91	-0.124	1.180	0.200	0.221
CMS	91	-0.100	0.120	-0.036	0.045
Biocheck-F	91	-0.225	0.000	-0.062	0.057

Table C.2. Frequency distribution (counts and percentages) of units by type of task.

Variable	Type	Frequency	%
Operation	1	59	64.
	2	9	9.
	3	4	4.
	4	13	14.
	5	6	6.

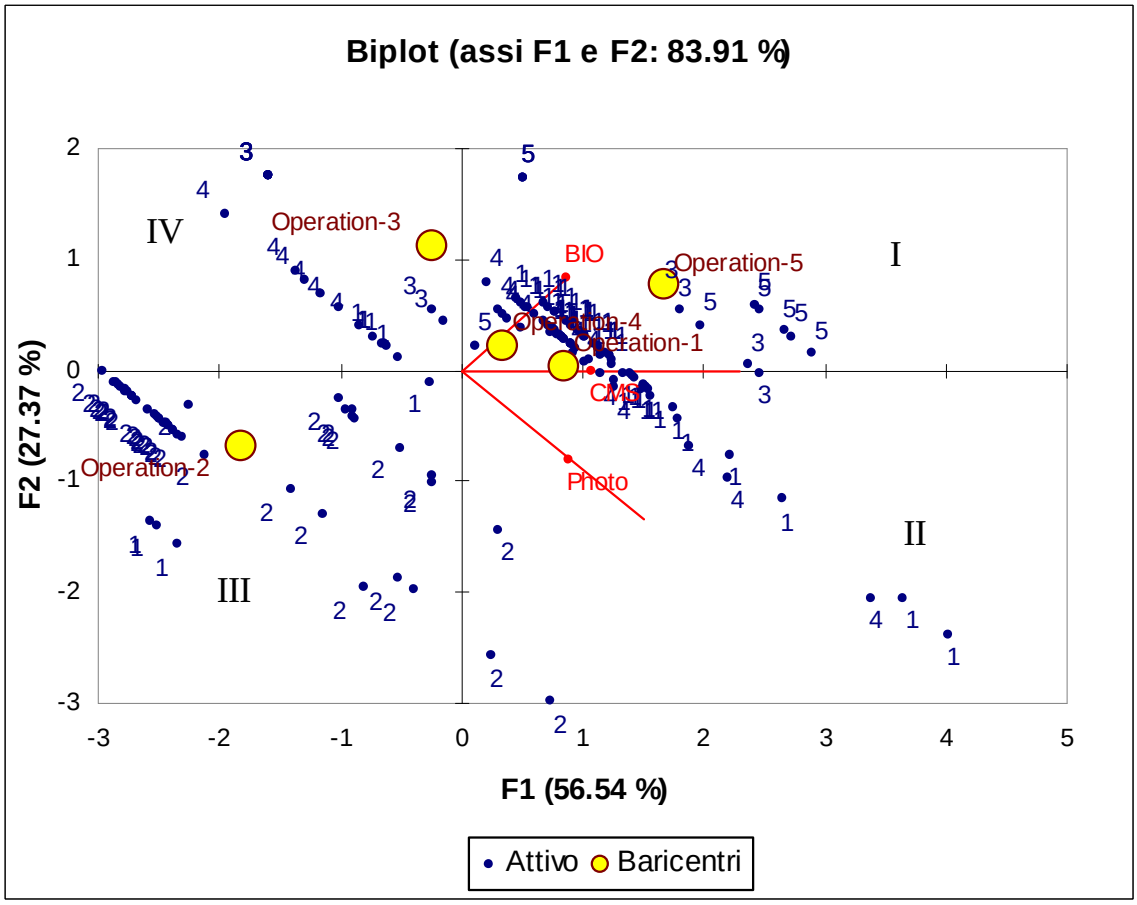
The *biplot* is a good representation of the three dimensional matrix since the cumulative variability explained by two factors is almost 84% of the total variability.
The vectors named *Bio* (Bio check F sampler), *CMS* (CMS sampler) and *Photo* (photo-acoustic monitor) show in graphic the correlation matrix below:

Correlation matrix (Spearman):			
Variables	*Photo*	*CMS*	*BIO*
Photo	**1**	**0.430**	**0.179**
CMS	**0.430**	**1**	**0.419**
BIO	**0.179**	**0.419**	**1**
Bold values are different from 0 at α=0.05			

Bio-check F values are more positively correlated to CMS than to photo-acoustic results.

The origin of the graph is the TLV-C, therefore points in quadrants I and II of the figure have higher results than TLV-C, while points in the third quadrant have levels below the TLV-C for formaldehyde (0.3 ppm). Points in fourth quadrant have higher level in Bio-check F results and lower level of CMS and photo-acoustic results.

Figure C.1 biplot



In conclusion, looking at the average profiles of the tasks, most of exposure determined by any method during task 2 is below the TLV-C, while other tasks have different profiles. Tasks 1 and 4 vary along the photo-acoustic measurements, while the grouping of tasks seem to follow the classes of Bio-check F measurements (task.2 lower followed by task 1, 4 and 3, 5 highest).

Appendix D

INDEX-UPRIC Project

Results of literature review

Table D.1 Human and animal studies and in-silico models

a. Human studies, controlled conditions

EFFECT	STUDY	SUBJECT	EXPOSURE	OUTCOME	COMMENT
Discomfort (subjective)	Krakowiak et al. 1998	10 asthmatics with suspected respiratory sensitisation to HCOH + 10 healthy.	0.3 ppm (0.5 mg/m^3) for 2 h.	(+) all subjects reported sneezing, itching and congestion.	Due to infrequent calibrations of the exposure chamber, it is possible that concentrations exceeded 0.5 ppm at some point of the study.
	Lang et al, 2008	21 healthy subjects	4h each x 10 dd at different concentrations with and without peaks (4 x 15 min).	LOAELs: 0.3 ppm eye; 0.5 ppm nose. NOAELs after *adjustments for negative affectivity*: 0.5 ppm constant or 0.3 ppm with 0.6 peaks.	NOAELs proposed considering *negative affectivity* factors.
Irritation - eye, upper airways (objective)	Lang et al, 2008	21 healthy subjects	4h each x 10 dd at different concentrations with and without peaks (4 x 15 min).	LOAEL: 0.5 ppm with 4 x 1ppm peaks (eye irritation and blinking) NOAEL: 0.5 ppm constant or 0.3 ppm with 0.6 ppm peaks.	
Pulmonary function (FEV1 and FVC)	Krakowiak et al, 1998	10 asthmatics with suspected respiratory sensitisation to HCOH + 10 healthy.	0.3 ppm (0.5 mg/m^3) for 2 h.	(-) no significant pulmonary function changes in both groups.	Due to infrequent calibrations of the exposure chamber, it is possible that concentrations exceeded 0.5 ppm at some point of the study.
	Lang et al, 2008	21 healthy subjects	4h each x 10 dd at different concentrations with and without peaks (4 x 15 min).	(-) no significant changes in lung function NOAEL: 1 ppm	
	Ezratty et al. 2007	12 subjects with intermittent asthma or allergy to pollen.	0.5 mg/m^3 for 1 h in 2 separated days.	(-) no significant changes in lung function NOAEL: 0.5 ppm	
	Casset et al., 2006	19 asthmatic subjects	0.1 mg/m^3 for 30 min.	(+) FEV1 significantly higher after formaldehyde exposure (15% vs 11%, p= 0.046)	

EFFECT	STUDY	SUBJECT	EXPOSURE	OUTCOME	COMMENT
Asthma/ Hypersensitivity	Krakowiak et al, 1998	10 asthmatics with suspected respiratory sensitisation to HCOH + 10 healthy.	0.3 ppm for 2 h.	(+) transient increase of the nr. of leukocytes and in the permeability index of proteins recovered from nasal washings from both groups- suggesting transient non-specific nasal reaction. (-) no induction of specific allergic responses in either the upper or the lower respiratory tract.	Due to infrequent calibrations of the exposure chamber, it is possible that concentrations exceeded 0.5 ppm at some point of the study.
	Ezratty et al., 2007	12 subjects with intermittent asthma or allergy to pollen.	0.5 mg/m^3 for 1 h in 2 separated days.	(-) no significant deleterious effect on airway allergen responsiveness (no enhanced asthmatic effect)	A trend to a protective effect of formaldehyde was observed.
	Casset et al., 2006	19 asthmatic subjects	0.1 mg/m^3 for 30 min.	(+) patients developed an immediate bronchial response at significantly lower dose of mite allergen than after air exposure.	

b. Human studies, uncontrolled conditions

EFFECT	STUDY	SUBJECT	EXPOSURE	OUTCOME	COMMENT
Genotoxicity	Orsiere et al, 2006	59 pathology and anatomy workers after 1 day-exposure (or 8h)	<0.1-20.4 ppm (sampling 15 min) <0.1 -0.7 ppm (sampling 8h)	(+) increased frequency of monocentrometric micronuclei (MN) in peripheral lymphocytes (chromosomal loss). (-) no increase in DNA damage (repair process or induction of lesions) in peripheral lymphocytes.	*Aneugenic effect* of formaldehyde: all call lines derived from HCOH-induced rat tumours have been shown to be aneupoid. Results suggest that MN was a consequence of spindle disturbances (tubulin) and not a direct interaction with DNA.
Histopathological changes	Edling et al., 1988	75 plant workers exposed to formaldehyde.	0.1-1.1 mg/m^3 with peaks of up to 5 mg/m^3	25% of exposed workers had changes to nasal mucosa. Histological grading showed a significantly higher score for nasal lesion among exposed. No difference btw those exposed to wood dust and HCOH and only HCOH.	*Authors attribute histopathological changes to HCOH alone in the 0.1-1.1 mg/m^3 range*
Asthma/ Hypersensitivity	Krzyzanowsky M et al. 1990	298 children 5-15 y, 613 adults;		Increased prevalence rate of physician-diagnosed chronic respiratory disease (chronic bronchitis or asthma) in children exposed to HCOH btw 60-140 ppb. Some 10% decrement in PEFR was found for concentrations as low as 30 ppb (greater effect in asthmatic children). Data suggests non-negligible respiratory effects of prolonged exposure to HCOH even below 60 ppb. LOAEL 30 ppb	Greater association of the effects was found with ETS and HCOH. ETS possible confounder.
	Wilhelmsson B, Holmstrom M, 1992	66 plant employees exposed for a mean of 10 years	0.05-0.6 mg/m^3 (mean 0.26. No exposure to industrial solvents or dust.Ref.group: 36 community clerks exposed to 0.09 mg/m^3	Frequency of atopics in the exposed was found low (11%) compared to the controls (33%) and the general population of UK and Scandinavia (30%). An hypothesis is that a certain number of atopics had left the HCOH-exposed environment. HCOH seems to induce non-specific hyperreactivity in the airways (about 50% of those chronically exposed to moderate doses)	Authors believe that HCOH can induce, in certain cases, IgE-mediated type 1 reaction in the nose, but in most cases the annoying nasal symptoms are due to HCOH-induced hyperreactivity which can cause problems in about 50% of the population subjected to long-term exposure at levels described in the study.

c. Animal studies

EFFECT	STUDY	SUBJECT	EXPOSURE	OUTCOME	COMMENT
Histopathological/biochemical changes in nasal tissues.	Cassee, 1996	Rat	1 and 3 day nose-only inhalation 6h/day at levels of 1.0, 3.2 and 6.4 ppm.	*3dd exp* -1.0 ppm: no changes -3.2 ppm: disarrangement, focal necrosis, thickening and desquamation of degenerated cells, hyperplasia of basal cells and increased number of mitotic figures. Significant increases of ULLIs at cross level II (index for cell proliferation), increased GPx activities.	
	Andersen et al. 2008	Rat	1)Exposures to 0, 0.7 2 and 6 ppm 6h/day, 5dd/week for 3 weeks. 2)Single 6h exposure adding groups for 15 ppm inhalation (compared with instillation of 40 µl of 400mM HCOH solution).	-0.7 ppm: inflammatory infiltrate observed; neither cell proliferation nor histopathology. -6 ppm: cell proliferation observed.	Mean daily concentrations of HCOH in the inhalation exposures were 15-20% less than target concentrations. The most sensitive responses of the epithelium to inhaled HCOH, in the range of 0.7-2 ppm, are likely to be associated with excursions of extracellular HCOH, leading to preferential interactions with targets on cell membranes or in the extracellular components
	Nielsen et al, 1999	Mouse	Range: 0.2-13 ppm for 30 min	RD10: 0.3 ppm (adopted as NOEL).	
Pulmonary function	Nielsen et al, 1999	Mouse	Range: 0.2-13 ppm for 30 min	RD50s: 3.1-5.3 ppm for decrease in respiratory rate. RD10: 0.3 ppm (adopted as NOEL).	No bronchocostriction observed at the low concentration range.

EFFECT	STUDY	SUBJECT	EXPOSURE	OUTCOME	COMMENT
Genomic	Andersen et al. 2008 Genomic benchmark dose analysis was performed	Rat	1)Exposures to 0, 0.7 2 and 6 ppm 6h/day, 5dd/week for 3 weeks. 2)Single 6h exposure adding groups for 15 ppm inhalation (compared with instillation of 40 µl of 400mM HCOH solution).	Btw 0.7 and 2 ppm: temporal and concentration dependent transitions in genomic signatures. Reduced sensivity by day 15 (*Tissue adaption*). U-shaped dose responses were noted in the acute study for many genes.	

d. In-silico models

AUTHOR	TITLE/TOPIC	POPULATION/STUDY DESIGN	MAIN FINDINGS	COMMENTS
(Conolly et al. 2004)	Application of the dose-response computational model to humans for the prediction of airway cancer risk.		Switch in additional risk curve between 0.6-0.7 ppm occurs. Direct mutation does not play a significant role. Moreover DPX do not accumulate in the rat (and humans) with repeated daily exposure. Additional risk for 80 years of continuous environmental exposure to 0.1 ppm of HCOH of 10^{-6} or less for respiratory tract carcinogenicity is driven by parameter considering DPX, since 0.1 ppm inhaled HCOH does not affect cell proliferation (cytotoxicity).	This model is considered (by authors themselves) to be based on risk-conservative choices.
(Conolly et al. 2003)	Biological motivated computational model to predict dose-response behaviours at exposure levels below those at which SCC were seen experimentally. (6 ppm and above)		Carcinogenicity of inhaled HCOH in rats appears to arise primarily from enhanced cell proliferation due to cytotoxic responses rather than from a mutagenic potential of the DNA-protein cross-links.	

Table D.2. Formaldehyde evaluations and exposure limit proposals

a. Non-cancer effects

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
INDEX Project, 2005	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, dysplasia	LOAEL for nose and throat irritation: 0.1 mg/m3 (WHO, 2000)	30 μg/m^3 (OEHHA, 1999, derivation from Wilhelmsson and Holmstrom, 1992; supported by Edling, 1988)	10 x 3 Intraspecies and children	E.L.: 30 μg/m^3 The observed acute effects and endpoints are consistent with the pathology seen in long-term studies; consequently, no distinction has been done between short-term and long-term ELs.
Arts, 2008		The LOAEL of INDEX 2005 was taken from WHO report stating that the lowest concentration associated with nose and throat irritation is 0.1 mg/m3 and 0.6 mg/m3 for eye irritation: in volunteer studies when assessed at the same time eye irritation was reported at levels lower than nose or throat irritation (reviewed by Paustenbach, 1997 and Arts, 2006). Eye irritation has been considered the most sensitive effect induced by formaldehyde even from SCOEL (SCOEL, 2007) 'it is very difficult, if not impossible, to appreciate subjective findings of respiratory and eye irritation in workers and the general population,' 'exposure-effect concentrations are not exactly known, and peak concentrations rather than average concentrations might have caused these effects (sensory irritation)'	'*Although there seems to be (some) variation between individuals in the reported sensory irritation response, this certainly was not with a factor of 10 for inter-individual difference within a specific study*'. These differences may be the result of bias, former experience, and or perception and affectivity rather than due to real differences in sensory irritation (Lang et al., 2008). With regards to asthmatic vulnerability it has been reported in several studies that no respiratory effects were observed when exposed to levels up to 2 ppm (Witek et al., 1987, Harving et al., 1990; Ezratty et al., 2007). Only at concentrations of 3 ppm significant changes in lung function were reported in asthmatic volunteers (Sauder et al., 1987). The presence of many confounders in available studies in children such as cigarette smoke and other irritant volatile organic chemicals, humidity, lack of sleep, and the overall subjectivity of the studies make it difficult id not impossible to determine the real causative agent.	It is concluded that an indoor air level of 0.1 ppm (0.12 mg/m3) formaldehyde, as indicated by Appel et al. (2006) can be considered a safe and appropriate level.

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
Arts, 2008	Eye and nose and throat irritation (sensory irritation	1200 μg/m^3 for sensory irritation (in general)-based on Lang		5 for intra-species variability justified based on the available data (Appel et al. 2006). No sensitive groups identified. It seems that this factor of is meant for humans in general, and is not worker-specific. Due to a more homogeneous population, the intra-species factor for workers may even be lower. In an extensive review on upper respiratory tract and ocular irritant effects of volatile chemicals a higher susceptibility of children was not mentioned (Doty et al., 2004). Based on the available data no additional assessment factor is needed. Appel et al, 2006 concluded that although in children higher internal concentrations can be reached because of the higher breathing rate and an incomplete metabolism, there is yet no indication that this also true for locally acting substances as formaldehyde. They therefore stated that it is not necessary to include an additional child-assessment factor. No sensitive groups identified	Indoor settings: 0.1 ppm considered safe for preventing any adverse effect. ('considered safe realistic and meaningful level, while still taking into account the carcinogenicity of formaldehyde').

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
Paustenbach, 1997	Irritation (eye, nose, throat). Sensitization Bronchoconstriction Total of 150 studies evaluated.	1200 μg/m^3 for eye. 'If irritation occurs at <1 ppm the effects rapidly subside due to accommodation'. LOEL: < 360 μg/m^3 for 3-8 h exp. LOAEL for bronchoconstriction>2 ppm.	NOEL: 360 (up to 8h/d exposure)	The panel recognized that there is some uncertainty in the margin of safety inherent 1.0 ppm per 8 h, since the basis is derived from relatively small studies of healthy volunteers. No sensitive groups identified 'Repeated exposure may not enhance susceptibility to formaldehyde'.	OEL: 360 μg/m^{3}is recommended as TWA (would protect nearly all workers except perhaps the 95th to 99th percentile person from transient eye irritation). Ceiling:1 ppm ('likely to protect at least 75% and perhaps as much as 95% of workers). For indoor settings levels below 0.1 ppm should prevent irritation in virtually all persons. Based on the available data the panel concluded that although concentrations below 0.1 ppm in residential setting have been reported to cause minor irritant effects in humans, based on the data obtained in volunteer studies, it is likely that this level of response was attributable to other environmental factors, the background incidence of eye irritation, self-selection bias, or the effects of interviewer interaction.
IAQ – WHO (2000)	Nose and throat irritation in humans after short-term exposure	100 μg/m^3 The lowest concentration that has been associated with nose and throat irritation in humans after short-term exposure is 10, mg/m3, although some individuals can sense the presence of formaldehyde at lower concentrations.			100 μg/m^3 (30-minute average) * although some individuals can sense the presence of FA at lower concentrations * exposure level at which there is a negligible risk of upper respiratory tract cancer in humans.
HEALTH CANADA: Proposed residential indoor air quality guidelines for formaldehyde (2005)	Short-term Effects - irritation of the mucosa of the upper respiratory tract and the eyes. (Kulle et al. 1993) Chronic Effects Other Than Cancer hospitalization for asthma in children (Rumchev et al. 2002),	1230 μg/m^3	615 μg/m^3 50 μg/m^3	10	123 μg/m^3 - (1-hour averaged) 50 μg/m^3 - (8-hours averaged) * development of allergic sensitization and/or asthma is biologically plausible as it is consistent with observations in animals.

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
					* the risk of cancer associated with FA levels sufficiently low to prevent irritation and inflammatory responses appears therefore to be negligible.
AFSSET, French IAGV (2007)	Acute: irritation of the respiratory tract and infraclinical inflammation (ATSDR 1999 evaluation based on Pazdrack et al. 1993.) Chronic: histopathological lesions in the nose (ATSDR 1999 evaluation based on Holmstrom et al., 1989)	500 μg/m^3 300 μg/m^3		10 10 x 3 intra-species variability and use of a LOAEL	50 μg/m^3 (2 hours). * also protecting against other suspected effects, such as respiratory function impairment. 10 μg/m^3 (for long-term exposure)
RIVM, guideline values for the indoor environment (2007)	RIVM 1995: eye, throat and nose irritation in humans		120 μg/m^3	100 used in 1995 for TCA: 1 target value in air - annual average. The question arises how much need there is for the relatively large safety margin (factor 100) used in 1995. There is a large variation between individuals in the human population in terms of the sensitivity to sensory irritation by FA. Some individuals only experience a reaction at concentrations exceeding 1 mg/m^{3}while others are sensitive to significantly lower concentrations; some susceptible individuals may experience discomfort at lower concentrations. It is not possible to give a reliable estimate of the concentration below which this will not occur. In conclusion, given the minor critical effect (sensory irritation), it would appear that the safety factor applied in 1995 might be rather high.	Maximun permissible risk: 120 μg/m^3 as the 30 minute average 10 μg/m^{3}as the annual average. * this is with the proviso that certain sensitive individuals may suffer irritation even at levels below the MPR
OEHHA, 2008	Eye irritation	1200 μg/m^3 Benchmark concentration (as BMCL05) : 0.44 ppm On eye irritation (based on Kulle et al 1987)	600 μg/m^3	-factor of 10 for toxicodynamics (intraspecies), for potential in asthma exacerbation, in children. The factor is inclusive of exacerbated effects on contact lens wearers	Acute REL 55 μg/m^3 (44 ppb) A possible mechanism explaining the association HCOH exposure-asthma is given. Genetic variation among individuals in the alcohol dehydrogenases (as ADH3-which is GSNOR) affects individual responses to HCOH. Unexpected variability was observed

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
					for bronchoconstriction and airway hyperreactivity. Although human studies investigating asthma, atopy or hypersensitisation due to HCOH exposure are not entirely consistent with each other (potential for confounding in each), taken together they suggest that children may be more sensitive to HCOH toxicity than adults.
	Obstruction and discomfort, lower airway discomfort, eye irritation.		90 μg/m^3 Based on Wilhelmsson and Holstrom 1992 (exposure of the reference group)	-factor of 10 for toxicodynamics (intraspecies), for potential in asthma exacerbation, in children.	8-hour REL 9 μg/m^3 (7 ppb)
	Increased pulmonary resistance	1200 μg/m^3	0.59 ppm based on Swiecichowski et al, 1993 (guinea pigs)	Cumulative uncertainty factor: 60 - Interspecies factor of 6 for toxicokinetic (adjustment to Human Equivalent Concentration) -factor of 10 for toxicodynamics (intraspecies), for potential in asthma exacerbation, in children.	8-hour REL 10 μg/m^3 (8 ppb)
	Obstruction and discomfort, lower airway discomfort, eye irritation.		90 μg/m^3 Based on Wilhelmsson and Holstrom 1992 (exposure of the reference group)	-factor of 10 for toxicodynamics (intraspecies), for potential in asthma exacerbation, in children.	Chronic REL 9 μg/m^3 (7 ppb)
	Asthma symptoms (cough, shortness of breath, wheeze, trouble breathing)	60 μg/m^3	30 μg/m^3 (lower limit of NOAEL range) Based on Rumchev et al., 2002 (asthmatic children)	Intraspecies factor of $\sqrt{10}$ (3.16) for potential toxicodynamic variability (inter-individual variation)	Chronic REL 10 μg/m^3 (8 ppb)

b. Considering carcinogenic effects

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
Appel, 2006	\	240 μg/m^3 A slight sensory irritation response can be observed at concentrations of 0.2 – 0.3 ppm and ocular and upper respiratory tract sensory irritation is not present below 0.1 ppm	120 μg/m^3		120 μg/m^3 (0.1 ppm) * Since 0.1 ppm is more than 10 times below the threshold level observed for cytotoxic damage in the nasal mucosa, this level seems to protect the whole population with regard to the carcinogen.
Arts, 2006	Sensory irritation (eye, nose and throat)-volunteer studies; Nasal injury - animals. Carcinogenicity - animals, population studies.	LOAEL for sensory irritation (humans): 1 ppm for eye, and 2 ppm for nasal and 3 ppm throat. Threshold for increased nasopharyngeal cancer risk in humans: 4 ppm (Hauptmann et al., 2004). Formaldehyde considered carcinogenic at cytotoxic levels only, i.e. levels at which sustained regenerative epithelial proliferation is observed ≥ 6 ppm in animals. Animals: NOAEL for nasal injury: 1 ppm LOAEL for epithelial hyperplasia and squamous metaplasia: 2 ppm BMD analysis performed on Andersen and Mohave 1983, Kulle 1993, Kulle et al, 1987. For 10% extra risk for mild eye irritation is accepted, 0.56 ppm (C.I. 95%) would be acceptable. At level of 1 ppm: -56% (C.I. 95%) experiences 'slight discomfort' after 2.5 h.		No sensitive groups identified (no asthma correlation, nor enhanced effects on asthmatic subjects).	Airborne levels of formaldehyde below 1 ppm seem low enough to protect workers against nasal tissue damage, consequently against the potential risk of nasal cancer

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
		-0% experiences 'discomfort' -30% (C.I. 95%) experiences 'mild eye irritation' 9.5% (C.I. 95%) experiences 'moderate eye irritation'			

c. Occupational exposure limits

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
Occupational exposure limit for Quebec workers. (Noisel, Bouchard and Carrier 2007)	Irritation can cause an irritant-induced asthma reaction and induce cytotoxicity that can act as a cancer promoter. The experimental data show that there was no difference in the proportion of individuals experiencing effects in groups exposed to FA concentrations	LOAEL : 1 ppm Benchmark concentration (as BMCL05) : 0.44 ppm on eye irritation based on Kulle et al 1987	NOAEL : 0.5 ppm	asthmatics did not appear to be more sensitive to irritation at FA concentrations below 3 ppm .	the risk of irritating effects would be negligible for airborne formaldehyde concentrations below 0.75 ppm.
SCOEL: Occupational exposure limits (Bolt and Huici-Montagud 2008)	Subjective symptoms of eye irritation (based on Lang, 2008) if the personal trait of negative affectivity was treated as a co-variable.		360 µg/m^3	The TWA-OEL of FA should be set at or below the NOAEL for sensory irritancy of the eye. In view of the limited number of persons that can be examined in a laboratory volunteer study, the exclusion of particularly sensitive persons with negative affectivity appears problematic.	480 µg/m^3- 15min-STEL This STEL is set below the threshold for objective eye irritation, as outlined by Lang At these levels, no systemic effect of formaldehyde is to be expected 240 µg/m^3 - 8h-TWA This especially considers possible interindividual differences in susceptibility to irritation by formaldehyde Additional classification: skin sensitizer.

d. Outdoor exposure limits

AUTHOR and YEAR	HEALTH EFFECTS	LOAEL	NOAEL	UNCERTAINTY FACTORS	EXPOSURE LIMIT
RA for the general population in Japan(Naya and Nakanishi 2005)	Histopathological changes (i.e., loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia) in the nasal cavity (Holmstrom et al., 1989)	50 μg/m^3 The lowest concentration of 0.04 ppm in the study of Holmstrom et al. is considered to be nearly equal to NOAEL;		3 for human LOAEL.	12 μg/m^3 Reference value of FA in atmosphere (outdoor air) for Japanese general population is recommended