

Development of carcinogenicity classifications and evaluations: the case of formaldehyde

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Summary. In this paper carcinogenicity classification and evaluations case of formaldehyde made by national and international agencies and organizations (such as European Union, International Agency for Research on Cancer, World Health Organization) both in occupational (such as American Conference of Government Industrial Hygienists, National Institute of Occupational Safety and Health and Occupational Health and Safety Administration) and non occupational environment (such as United States Environmental Protection Agency) are proposed. The differences in the database and consequently in the conclusion are described in a short historical review since formaldehyde was considered for the first time as regard as health effects.

Key words: formaldehyde, carcinogenicity, evaluation, classification and labelling, limit values, criteria.

Riassunto (*Sviluppo delle classificazioni e valutazioni di carcinogenicità: il caso della formaldeide*). In questo lavoro vengono proposte le classificazioni e valutazioni di cancerogenicità relative alla formaldeide emesse da agenzie e organizzazioni nazionali e internazionali quali Unione Europea, International Agency for Research on Cancer, World Health Organization, sia relative alla esposizione in ambiente professionale (American Conference of Government Industrial Hygienists, National Institute of Occupational Safety and Health and Occupational Health and Safety Administration) sia a quella in ambiente non professionale (quali valori dell' United States Environmental Protection Agency). Vengono riportate in una breve rassegna storica le differenti modalità di gestione dei dati, e le differenti conclusioni, cui sono pervenuti enti e organizzazioni a partire da quando la formaldeide è stata presa in considerazione per la prima volta per i suoi effetti sulla salute.

Parole chiave: formaldeide, cancerogenicità, valutazione, classificazione ed etichettatura, valori limite, criteri.

INTRODUCTION

It is particularly interesting to observe the development of the assessment which organizations and national and international agencies make regarding chemical substances and their related risks, as a consequence of the broadening of scientific knowledge, production of new studies and the updating of evaluation criteria.

In particular, a valuable example is represented by formaldehyde, and this review aims to illustrate classifications, guidelines, limit values, standards and criteria of acceptability of exposure in the environment and workplace, proposed by regulatory government organizations such as the European Union (EU), the United States Environmental Protection Agency (US EPA), the United States Department of Health and Human Services (US DHHS) and the United States Occupational Safety Health Administration (US OSHA), national advisory agencies and commissions, such as the Commissione Consultiva Tossicologica Nazionale (CCTN), international independent scientific institutions such as the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), the International Programme on Chemical Safety (IPCS), the National Institute for Occupational Safety and Health (NIOSH) and the European Centre for Ecotoxicology and Toxicology

of Chemicals (ECETOC). The evaluations issued by NTP, EPA, CCTN, IARC are not legally binding in each European country but represent a scientific reference in handling environmental issues.

In this review updated classification and evaluation are integrated with suggestions on previous evaluations including, where available, a short historical analysis of their development. Among other things, the progressive investigations of the issue have brought about a reduction of the limits of exposure which, in the case of ACGIH, was of three orders of magnitude, from the initial 10 (ppm) to the current 0.3 (ppm); it is also worth noting that the 0.016 ppm REL-TWA of NIOSH is significantly lower than the 0.75 PEL-TWA of the OSHA.

EUROPEAN UNION CLASSIFICATION

Formaldehyde was first added to the list of dangerous substances of the EU (Annex I of directive 67/548/EEC) in 1976, with amendments in 1981, 1987, 1994 e 2005:

- *EU 1976 classification.* In 1976 the substance had two classifications, one related to "formaldehyde solution between 5 and 30% considered irritant (Xi) with risk phrase R36/37: "irritant for the eyes and

respiratory tracts”, and one related to formaldehyde solutions with concentrations greater than 30%, considered toxic (T) with risk phrase R23/24/25: “Toxic by inhalation, in contact with skin and if swallowed” [1]. In 1976 there was still no single criteria for classification of substances as carcinogenic but, as a consequence of adverse effects on health, they were classified as “toxic”, “harmful”, “corrosive” or “irritant”;

- *EU 1981 classification.* In 1981 the classification of the two solutions with different concentrations were integrated with the addition of risk phrase R43: “may cause sensitivity due to contact with skin” [2];
- *EU 1987 classification.* The 1987 revision introduced in the classification the carcinogen category 3: “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” with risk phrase R40 “Limited evidence of a carcinogenic effect” ascribed on the basis of studies on experimental animals [3];
- *EU 1994 classification.* The latest revision (1994), currently in force, presents a single description related to formaldehyde aqueous solution which is classified as: carcinogen category 3; toxic (T) with risk phrase R 23/24/25: “toxic for inhalation, ingestion and contact with skin”; corrosive (C) with phrase R 34: “causes burns” and “sensitizing” with phrase R 43: “may cause sensitization by skin contact”, furthermore ascribing new specific concentration limits for the classification of preparations which contain formaldehyde; a lower level, 0.2% vs. 1%, being adopted for sensitization [4].

Discussions are under way for a new classification of formaldehyde as a result of the IARC review of the epidemiology [5]. France is the “Rapporteur”, called on to draft a new classification for the EU, hereby presented along with comments from other stakeholders.

BASIS FOR THE NEW CLASSIFICATION PROPOSED BY FRANCE AS PART OF THE EU WORKING GROUP “CLASSIFICATION AND LABELLING OF DANGEROUS SUBSTANCES” (JULY 2005)

The current classification for health effects had not been revised until 2005 when, following revision by IARC [5], upon request of various Member States, formaldehyde was put on the agenda of the Working Group “Classification and Labelling of Dangerous Substances”. France, Rapporteur Country, proposed classifying it in category 1 with the risk phrase R49: “may cause cancer by inhalation” based on induction of nasopharyngeal cancer and based upon the same epidemiologic studies used by IARC for the new classification [6].

In the French classification proposal, the evidence for a causal association between exposure to formaldehyde and induction of nasopharyngeal cancer is based on:

- positive association which essentially is revealed by

the large and wide updated industrial cohort study of the National Cancer Institute (NCI) [7];

- further supporting evidence from several independent epidemiological studies, case-control studies and meta-analysis of the one produced by the NCI and which also reveal elevated risk [8-13];
- biologic plausibility based on laboratory experiments conducted on animals which demonstrate induction of cancer in rats by inhalation of formaldehyde in the nasal tract with a clearly identified mechanism which leads to chronic irritation, cytotoxicity, proliferative regeneration and tumour formation. It has been widely recognized that man is more sensitive to irritation of the upper respiratory tract induced by formaldehyde and these data demonstrate a plausible biologic mechanism for induction of nasopharyngeal cancers in man.

The French proposal also mentions several other epidemiologic studies which are negative or in which mortality due to nasopharyngeal cancers was not significant [14-17], however the French experts do not consider them such as to modify the proposed classification of formaldehyde in category 1, formulated as follows: “In conclusion, epidemiologic studies show an elevated risk for tumour induction at the site of contact by inhalation of formaldehyde with a convincing body of evidence to establish a causal relationship for nasopharyngeal cancers. Observation of an increased tumour incidence at the site of contact in rats with a mechanism of chronic irritation and sensitivity of humans to irritation of the upper respiratory tract following formaldehyde inhalation provide biological plausibility and strengthen the weight of evidence of human carcinogenicity. In rats, tumour induction is associated with cytotoxicity and regenerative cell proliferation as a predominant feature with a clear threshold and it should therefore be noted that a threshold is also likely in humans” [6]. The latter consideration is in agreement with what reported by the World Health Organisation (see below).

Subsequently to the French proposal, FormaCare (group instituted by European producers of formaldehyde as official representative of European formaldehyde producers) highlighted the complexity of available epidemiologic data and the need to approach analysis with caution [18]. However, considering that:

- the current epidemiologic data are not conclusive;
- the basis of epidemiologic data is substantially unmodified with respect to that assessed by IARC in 1995 in spite of being updated by three large cohorts [7, 14, 15];
- the carcinogenic data on experimental animals are substantially unmodified after the initial IARC evaluation in 1982 and the EU evaluation in the early ‘80s;
- it would be useful to delay discussion until the beginning of 2007 when data related to analysis of mortality in the cohort studies of NCI, currently in progress, which examines 10 further years of mortality will be available;

the FormaCare has continued to uphold the current classification as carcinogen category 3 [18].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Carcinogenicity of formaldehyde has been evaluated by the International Agency for Research on Cancer (IARC) several times. The first evaluation was conducted in 1981 [19], and updated in 1982 [20], 1987 [21], 1995 [22] and finally in 2004 [23]. The most recent evaluation moves formaldehyde from the group of “probably carcinogenic for humans” (group 2A) in which it was placed in 1987, and reconfirmed in 1995, to that of “carcinogenic to humans” (group 1) on the basis of induction of nasopharyngeal cancer while there is still uncertainty (“strong but not sufficient evidence”) of causal association with myeloid leukemia and a limited one for nasopharyngeal carcinoma of paranasal cavities [23]. The new evaluation will be published on IARC monograph volume 88, (in print), though the Working Group for volume 88 has published the summary of the monograph [24]:

- *IARC 1982 evaluation.* Evidence that formaldehyde in its gaseous form were carcinogenic among rats was considered sufficient while epidemiologic studies provided inadequate evidence to determine carcinogenicity of formaldehyde in man [19]. In October of the same year, IARC published a supplement to monographs released until then (volumes 1 to 29) in which formaldehyde in gaseous form was listed among those probably carcinogenic to humans (group 2B) on the basis of data contained in monograph 29, due to inadequate evidence of carcinogenicity to humans, sufficient to animals and, furthermore, sufficient evidence in short term experiments [20];
- *IARC 1987 evaluation.* Formaldehyde was placed among the group of substances “probably carcinogenic to humans” (group 2A) on the basis of “limited evidence” for the carcinogenicity to humans and “sufficient evidence” in experimental animals [21];
- *IARC 1995 evaluation.* Formaldehyde was placed among the group of substances “probably carcinogenic to humans” (group 2A) on the basis of limited evidence for the carcinogenicity to humans and “sufficient evidence” in experimental animals found in more recent studies compared to those considered previously [22].

Basis for the more recent IARC evaluation (2005). IARC has concluded that in humans there is sufficient evidence to establish a causal association between exposure to formaldehyde and nasopharyngeal cancers. This conclusion is mainly based on statistically significant reports of increased mortality from nasopharyngeal cancer which emerge from the update of a large cohort of US industry workers published by NCI [7], along with similar studies of other cohorts, or of embalmers [25] and the other cohort of workers for companies which manufactured or used formaldehyde [26], and to an elevated risk in five out of seven case-control studies [8-13, 27]. Although other cohorts reported few cases of nasopharyngeal cancer compared to the number expected [14, 15, 28], the IARC Working Group observed that the differences

were small and the studies taken into consideration had low power to detect effect on nasopharyngeal cancer, and that it was “improbable that all of the positive findings for nasopharyngeal cancer that were reported from the epidemiological studies, and particularly from the large study of industrial workers in the USA, could be explained by bias or unrecognized confounding effects”. Overall, the Working Group concluded that the results of the study of industrial workers in the USA provided “sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans”.

UNITED STATES NATIONAL TOXICOLOGY PROGRAM

The United States National Toxicology Program (US NTP) Report on Carcinogens (RoC) published by the Department of Health and Human Services lists, starting from 1981 (second Annual Report), formaldehyde in its gaseous state in the category of “reasonably anticipated to be a human carcinogen”. This classification is based on carcinogenicity data found in IARC monographs (1982, 1987, 1995), in particular on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals [29].

In a notice published on the Federal Register on October 18, 2005, NTP designated formaldehyde in light of its possible reconsideration for inclusion in the 12th RoC as “known to be human carcinogen” (substances for which there is sufficient evidence of carcinogenicity), derived from epidemiologic studies which indicate a causal relationship between exposure to the agent, as such or as a compound, and cancer in humans [30]. This designation is based on IARC’s reassessment in 2004.

COMMISSIONE CONSULTIVA TOSSICOLOGICA NAZIONALE

On the session of June 1, 1981, the national toxicological advisory commission (Commissione Consultiva Tossicologica Nazionale, CCTN), at the time called Commission for the study of cancerogenic, mutagenic and teratogenic effects of chemical compounds, called on to express an opinion on health risks connected to possible uses of formaldehyde, concluded that “the experimental data currently available suggest the possibility of cancerous risk in humans due to inhalation. Furthermore, a genetic risk can be assumed. However, the data are mostly described as preliminary and refer to inconclusive research; they are therefore not sufficient to clearly define the type or degree of toxicological risks. Pending acquisition of final and detailed results of recently completed toxicological studies, and the results of epidemiologic studies under way, the Commission feels it is necessary to acquire information regarding the levels and modes of exposure, especially by inhalation, for workers as well as for the population in general, and that the necessary steps be taken to reduce exposure” [31]. At that time IARC had

not yet published its first evaluation and epidemiologic research on cohorts of workers in the US and in the UK were expected shortly. Results of three cohorts (one on embalmers and two on chemical industry workers) which were at the time available, and which revealed an excess of some types of tumours, however revealed methodological limits and various types of exposure, characteristics which made them, while compatible with an excess of risk of exposure to formaldehyde, inconclusive.

In June 1984, the CCTN Commission, working on the same query proposed in 1981 related to health risks connected to possible use of formaldehyde, in light of newly acquired documentation and that available in 1981, placed formaldehyde in category 1b (substances with sufficient evidence of experimental carcinogenicity and with not determinable epidemiologic evidence) on the basis of published data [32]. In particular, the Commission highlighted in its opinion that “in humans cancerogenic risk by inhalation remains a possibility and it is imperative to seek to reduce as much as possible exposure to formaldehyde among workers as well as among the population in general” [32]. At the time of this evaluation the evaluation expressed by IARC in 1982 was available.

In 1991, in agreement with the new classification criteria approved in 1990, the substance was moved to the new category 2 of carcinogenicity (substances for which, based on adequate long-term studies carried out on animals and/or on other specific information, there are elements sufficient to determine that exposure can lead to cancer in humans) with no revaluation on the basis of experimental as well as epidemiologic data [33].

In 1996 the classification in category 2 of carcinogenicity was reconfirmed [34]. In particular, regarding epidemiologic studies, the confirmation was based on what reported below [35]:

- occupational exposure to formaldehyde proved to be associated with an increasing risk of rhinopharyngeal cancer in some cohorts and case-control studies. In particular, a cohort [36] related to ten plants where formaldehyde was produced or used demonstrated a relation between rhinopharyngeal cancer and cumulative exposure. In case-control studies, the risk is particularly high in categories with higher exposure, and as a consequence of a twenty-year period of induction-latency, and cannot be explained by confounding factors such as occupational exposure to wood dust and the habit of smoking;
- two meta-analyses lead to estimations of the risk of rhinopharyngeal cancer for those exposed to high levels of formaldehyde, respectively, of 2.1 (1.1- 3.5) and 2.7 (1.4-5.6) [37, 38];
- some case-control studies suggest an association between exposure to formaldehyde and the occurrence of squamous cell carcinoma in nasal and paranasal cavities;
- the IARC evaluation of 1995 is of limited evidence [22].
- following the publication of the IARC monograph,

a study was conducted on the incidence of different types of tumour among workers of 265 Danish firms in which formaldehyde was used; the study was carried out through a procedure of record-linkage between the National Tumour Registry and the Pension Fund [26]. For the malignant tumour of nasal and paranasal cavities a standardized proportional incidence relationship (SPIR) of 2.3 was calculated (CI 95%: 1.3-4.0, 13 observed cases); among subjects exposed to formaldehyde and not to wood dust the SPIR was 3.0 (1.4-5.7, 9 observed cases). The tumours examined are generally squamous and are, more frequently than expected, located in nasal cavities (excluding paranasal cavities): SPIR 2.9 (1.3-5.3, 9 observed cases).

The classification criteria used by CCTN is harmonized to that of the EU; therefore category 2 of CCTN corresponds to category 2 of the EU with risk phrase R45 [39].

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The International Programme on Chemical Safety (IPCS), collaborative programme of United Nations Environment Programme (UNEP), International Labour Office (ILO) and World Health Organization (WHO), in the Concise International Chemical Assessment Document published in 2002, regarding neoplastic effects, reports that The results of epidemiological studies in occupationally exposed populations are consistent with a pattern of weak positive responses for genotoxicity, with good evidence of an effect at site of contact (e.g., micronucleated buccal or nasal mucosal cells). Evidence for distal (*i.e.*, systemic) effects is equivocal. Overall, based on studies in both animals and humans, formaldehyde is weakly genotoxic, with good evidence of an effect at site of contact, but less convincing evidence at distal sites. Epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human cancer, although the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data. Therefore, based primarily upon data derived from laboratory studies, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans” [40]. The IPSC’s monograph refers to the evaluation and to the data contained in IARC’s 1995 monograph.

Previously, in 1989, in a monograph of the Environmental Health Criteria series, WHO concluded that “The available human evidence indicates that formaldehyde does not have a high carcinogenic potential. While some studies have indicated an excess of cancer in exposed individuals or populations, only nasal or nasopharyngeal cancer are likely to be causally related to formaldehyde exposure” [41]. IPCS’s monograph referred to the evaluation and to the data contained in IARC’s 1987 monograph.

EUROPEAN CHEMICAL INDUSTRY ECOLOGY AND TOXICOLOGY CENTRE

In 1981, European Chemical Industry Ecology and Toxicology Centre (ECETOC), organism which aims to coordinate scientific knowledge in the European industry, for the first time reviewed toxicology of formaldehyde [42, 43]. After examining data on its effects and on its potential as carcinogenic and mutagenic, ECETOC concluded that “the available epidemiologic data do not indicate any causal relationship between previous exposure to formaldehyde and the presence of malignant neoplasia in humans”

In its 1982 update [44], in light of new available studies and in particular of the CIIT/Battelle study [45, 46] of chronic inhalatory toxicity in rats, ECETOC claimed that “the nasal cancers observed in experimental animals develop only at concentrations which produce chronic tissue irritation. Where exposure is so low that metaplasia resulting from irritation does not occur, it is unlikely that cancer will develop. The new epidemiological data [47] confirm that there is no relationship between formaldehyde exposure and cancer in humans”. Also this monograph did not take into consideration the IARC monograph published in 1982.

In 1995 in a new technical report which evaluated carcinogenic risk of formaldehyde in humans, ECETOC concluded: “After a careful review of the cytologic, cytogenic and epidemiological studies there is no evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk. Causal criteria used by epidemiologists in evaluating an association, such as strength of an association, consistency of results across studies, dose response effects, biologic plausibility and coherence have not been met by the studies examined in this report” [48].

GUIDELINES FOR THE GENERAL POPULATION

US Environmental Protection Agency evaluation of carcinogenic risk

In 1991 the US EPA published a qualitative and quantitative evaluation of carcinogenic risk associated to oral and inhalatory exposure to formaldehyde [49]. This evaluation is finalized to the protection of the general population. Using criteria of the 1986 Guidelines for Carcinogen Risk Assessment [50] the agency placed the substance in the category of “probable human carcinogen” (group B1) on the basis of limited evidence in humans and sufficient evidence in experimental animals. The classification is based on nine studies on man, which however do not include Hauptmann’s 2004 study, at the time still not available, that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. Studies on mice and rats, exposed to long-term inhalation, revealed an increased incidence of nasal squamous cell carcinomas. The classification was furthermore supported by *in vitro* genotoxicity data

and formaldehyde’s structural relationships to other carcinogenic aldehydes such as acetaldehyde. That evaluation was never modified.

As for quantitative estimate of carcinogenic risk by inhalation, EPA carries out its evaluations based on experimental data indicating a inhalation unit risk equal to 1.3×10^{-5} for a life-time exposure equal to $1 \mu\text{g}/\text{m}^3$. This value was calculated from a study finalized to determine incidence of malignant nasal cancer in male F344 rats exposed through inhalation to different concentrations of formaldehyde for two years [51].

World Health Organization air quality guidelines

WHO established in 1987 a guideline value of air quality for the general population of $0.1 \text{ mg}/\text{m}^3$ ($100 \mu\text{g}/\text{m}^3$) as a 30-minute average recommended to avoid complaints among sensitive population to indoor air in non-industrial buildings [52]. With respect to carcinogenicity, WHO made reference to the IARC report which placed formaldehyde in its gaseous form in group 2B on the basis of inadequate carcinogenicity in humans and sufficient in experimental animals. However no risk estimate calculation is indicated because available animal data do not allow a reasonable use of existing models.

The revised WHO Air Quality Guidelines for Europe published in 2000 conclude that the predominant symptoms of exposure to formaldehyde in humans are irritation of the eyes, nose and throat along with discomfort, lacrimation, sneezing, cough, nausea, dyspnea and finally death depending on the dose and reconfirms the air quality guideline value of $0.1 \text{ mg}/\text{m}^3$ ($100 \mu\text{g}/\text{m}^3$) as a 30-minute average to prevent significant sensory irritation in the general population [53]. The basis for establishing this value is represented by the lowest concentration associated with nose and throat irritation in human after short-term exposure to concentration of $0.1 \text{ mg}/\text{m}^3$, although some individuals can sense the presence of formaldehyde at lower concentrations. In this updated version, WHO takes into consideration IARC’s 1995 evaluation which, as mentioned, classified the substance in group 2A and, regarding the carcinogenic risk, considered that “there is convincing evidence of high concentrations of formaldehyde being capable of inducing nasal cancer in rats and possibly in mice. There is also epidemiological evidence of associations between relatively high occupational exposure to formaldehyde and both nasopharyngeal and sinonasal cancers. Despite differences in the anatomy and physiology of the respiratory tract between rats and humans, the respiratory tract defence mechanisms are similar. It is therefore reasonable to assume that the response of the human respiratory tract mucosa to formaldehyde will be similar to that of the rat. Thus, if the respiratory tract tissue is not repeatedly damaged, exposure of humans to low, noncytotoxic concentrations of formaldehyde can be assumed to be associated with a negligible cancer risk. This is consistent with epidemiological findings of excess risks of nasopharyngeal and sinonasal cancers associated with concentrations above about $1 \text{ mg}/\text{m}^3$ ”.

In its conclusions, WHO reported that since this level is one order of magnitude higher than the threshold level for cytotoxic effects on nasal mucosa, the 0.1 mg/m³ (as a 30-minute average) guideline value represents an exposure at which risk of disturbances in respiratory tracts in humans is negligible.

US Agency for Toxic Substances and Disease Registry conclusion

In 1999, the US Agency for Toxic Substances and Disease Registry (ATSDR) of Department of Health and Human Services set minimal risk level (MRL) for formaldehyde for the protection of the general population chronically exposed by inhalation to 10-2 mg/m³ (0.008 ppm) [54].

The MRL value was derived from a 0.24 ppm (0.3 mg/m³) LOAEL for histological evidence of mild damage to the nasal epithelial tissue in formaldehyde exposed chemical workers [55]. An uncertainty factor of 30 was used (3 for the use of a LOAEL and 10 to take into account human variability).

LIMIT VALUES OF EXPOSURE IN WORKPLACES

US American Conference of Governmental Industrial Hygienists limit

The US American Conference of Governmental Industrial Hygienists (ACGIH) is a non-governmental professional association which currently published limit values of exposure to chemical and physical agents in workplaces (threshold limit values - TLV) which constitute an important reference of good technique at an international level. ACGIH TLVs are also recognized by some collective labour agreements, and are generally lower than PELs of OSHA.

Over the past years, the TLV of formaldehyde has changed repeatedly. The ACGIH took formaldehyde into account for the first time in 1946 and it has been reevaluated many times until it was assigned the current ceiling limit value (TLV-C) (maximum amount not to be exceeded in workplaces) of 0.3 ppm (0.37 mg/m³) established in 1992 [56]. This value modifies the 1 ppm TLV-TWA and the 2 ppm TLV-STEL set in 1985. Formaldehyde is furthermore classified as "suspected human carcinogen" (category A2) and is labelled "sensitizer". The TLV-ceiling was recommended to minimize the potential for sensory irritation, chiefly high and upper respiratory tract on the basis of evidence of irritation among individuals occupationally exposed and in other nonoccupational related areas such as mobile homes. According to ACGIH, this recommended TLV may not eliminate all the effects of sensorial irritation associated with exposure to the substance; however, the agency feels that this value should lead to a significant reduction in effects currently associated with exposure to formaldehyde. Category A2 is based on "the reports of several chronic animal inhalation studies in which exposed rats and mice displayed tumorigenic responses that included squamous metaplasia, papillary hyperplasia,

and squamous cell carcinomas of the nasal cavity. Although the epidemiological studies are equivocal or insufficient to confirm an increased risk of cancer in formaldehyde-exposed workers, the studies do not exclude the possibility of a formaldehyde-related cancer risk".

Chronology of limit values [56]

- In 1946 ACGIH recommended a maximum admissible concentration (MAC) of 10 ppm based on observation of irritation to skin and mucous membranes. In the United States, the term MAC was the predecessor to the acronym TLV.
- In 1948 a TLV-TWA of 5 ppm was adopted, to be valid until 1963, based on observation of irritation to eyes, respiratory tract and skin.
- From 1963 to 1971 the value was kept at 5 ppm, which however became a ceiling value (concentration not to be exceeded), based on irritation to eyes and respiratory tract reported at 5-6 ppm.
- In 1970 it was proposed to reduce the TLV-ceiling to 2 ppm.
- In 1972 the TLV-ceiling was reduced to 2 ppm and kept until 1984. This value is considered "adequate to prevent serious or persistent adverse effects".
- In 1981 it was proposed to lower the TLV-ceiling to 1 ppm and to designate it as an "A2 carcinogen" (substance suspected of carcinogenic potential to humans).
- In 1983, 1 ppm TLV-TWA, 2 ppm TLV-STEL and allocation in category A2 of carcinogenicity were proposed, on the basis of positive results in rats and mice exposed to concentrations of 2, 6 or 15 ppm for 30 hour/week for periods longer than two years [57].
- From 1985 to 1991 the following were valid: a 1 ppm TLV-TWA; a 2 ppm TLV-STEL and allocation in carcinogenicity category A2. According to the ACGIH Commission, a 1 ppm TLV-TWA should be adequate and no serious or persistent adverse effect should arise. This value might not be low enough to prevent irritation or disorders in hypersensitive individuals. Category A2 is ascribed on the basis of a carcinogenicity study in rats exposed by inhalation [51].
- In 1989, ACGIH proposed the reduction of ceiling value to 0.3 ppm on the basis of observation of irritation to the eyes and upper respiratory tract in individuals exposed in controlled inhalation studies, in workplaces, and in mobile homes. Formaldehyde continues to be placed in category A2 of carcinogenesis.
- From 1992 to date a 0.3 ppm ceiling limit and allocation in category A2 of carcinogenesis are valid.
- The label "sensitizer", proposed in 1999, was adopted in 2000.

US Occupational Safety and Health Administration limit

The US Occupational Safety and Health Administration (OSHA) establishes legally binding concentration limits for workers in occupational settings, based on review of

recommended levels of NIOSH. These levels are established for the “average” worker in a generally healthy condition. OSHA officially promulgates the list of concentration limits, which are termed permissible exposure limits (PELs). These are the legally binding limits that can not be exceeded in a working environment. These levels are established for workers in good health. OSHA may adopt or modify a REL proposed by NIOSH. There is usually a time lag between the proposal issued by NIOSH and the time they are officially promulgated as an official OSHA standard. This often leads to relevant differences between PEL values of OSHA and the REL values of NIOSH. The PEL values of OSHA are not used outside the USA.

The standards currently accepted for formaldehyde [58], amended on 26 June, 1992 are:

- the 8-hour PEL-TWA, defined as “average exposure of a worker to the environment which should not be exceeded in an 8-hour daily worktime and a 40-hour weekly worktime”, equivalent to 0.75 ppm;
- a second PEL, expressed as STEL (short-term exposure limit), of 2 ppm which is the maximum exposure allowed during a 15-minute period;
- a 0.5 ppm Action Level which corresponds to a concentration in air calculated as an 8-hour average, whose level is lower than PEL and for which specific respiratory protection procedures are required for workers, while, in case such level is exceeded, there is a requirement for specific procedures, such as medical surveillance and monitoring of the workplace in order to determine each worker’s probable exposure;
- formaldehyde is also considered a “potential carcinogen”.

The standards are based on a wide range of evidence originating from data on animals as well as from epidemiologic data. OSHA recognizes formaldehyde as a potential occupational carcinogen and suggests that exposure to the substance be regulated for its irritating and sensitizing effects on eyes, nose and throat. These standards refer to all the forms of formaldehyde, including mixtures and solutions containing formaldehyde in quantities of 0.1% or more, gas and materials capable of releasing formaldehyde in quantities greater than 0.1 ppm in workplaces.

Chronology of limit values

- In 1978, the Department of Labor of the OSHA set a maximum 8-hour TWA level of 3 ppm for formaldehyde, a 5 ppm ceiling concentration and 10 ppm as the maximum acceptable peak above the ceiling concentration for no longer than of 30 minutes totally per 8-hour daily work [57].
- In 1985 OSHA proposed lowering the existing permissible exposure limit (PEL) [59].
- On 4 December, 1987 OSHA reduced PEL from 3 ppm to 1 ppm on the average of 8 working hours considering formaldehyde a “potential carcinogen in humans” and set a STEL of 2 ppm. This reduction was in agreement with what recommended by NIOSH in 1981 [57]. In May 1992 the law was amended and the limit reduced to the current value of 0.75 ppm [58].

US National Institute for Occupational Safety and Health limit

The US National Institute for Occupational Safety and Health (NIOSH) is a federal agency, authorized by the Occupational Safety and Health Act of 1970 (29 USC Chapter 15) and the Federal Mine Safety and Health Act of 1977 (30 USC Chapter 22). NIOSH conducts research, drafts recommendations for the prevention of occupational diseased and accidents, evaluates toxicological studies and periodically recommends occupational standards called recommended exposure limits (RELs). It is wholly an advisory agency and its limits are “recommendations”, and OSHA is the only agency in the USA which still has legal authority to establish exposure limits. Once established and published, the REL values are forwarded to OSHA and to MSHA to be used in the enactment of legal standards. Also the REL values are generally lower than the PEL values of OSHA. The main difference between OSHA and NIOSH is that the former use an average over 8 hours, while the latter uses an average over 10 hours.

Currently NIOSH sets two types of recommended exposure limits (REL) for formaldehyde [61]: a REL-TWA (defined as average concentration for a 10-hour daily worktime and for a 40-hour weekly worktime) of 0.016 ppm and a 15-minute REL-Ceiling (defined as the value that should never be exceeded, not even for an instant) of 0.1 ppm.

It is worth noting that the 0.016 ppm REL-TWA is significantly lower than the 0.75 ppm PEL-TWA.

There are various data banks of substances used in workplaces and of the risks they pose, including the NIOSH Pocket Guide to Chemical Hazards and the International Chemical Safety Cards (ICSC), which NIOSH updates. The NIOSH Pocket Guide lists formaldehyde as “a potential occupational carcinogen” and the ICSC Card, in the section related to long-term effects or consequences of prolonged exposure, considers the substance “possibly carcinogenic in humans”.

Chronology of limit values

In 1976, NIOSH recommended, on the basis of irritant effects, that workers’ exposure to formaldehyde in occupational environment be controlled to a concentration no greater than 1.2 milligrams per cubic meter of air (1 ppm) for any 30-minute sampling period. [62]. At the time, the carcinogenic potential of formaldehyde was not known and therefore this end point was not considered in developing the recommendations.

In 1981 in a Current Intelligence Bulletin NIOSH recommended that formaldehyde be handled as a “potential occupational carcinogen” and that appropriate controls be used to reduce worker exposure. These recommendations were based primarily on a Chemical Industry Institute of Toxicology (CIIT) study in which laboratory rats and mice exposed to formaldehyde vapor developed nasal cancer, and are supported by a New York University study where rats

exposed to a mixture of formaldehyde and hydrochloric acid vapors developed nasal cancer. Furthermore, in several short-term laboratory studies, the substance was mutagenic [57]. Based on these results NIOSH concluded recommending stringent work practices and controls in order to reduce occupational exposure to the lowest feasible limit as much as possible even though it was not possible to estimate the extent of cancer risk among workers exposed to various levels of formaldehyde at or below the current 3 ppm standard.

CONCLUSION

This “historical analysis” highlights the evolution of the evaluations and classifications of formaldehyde in relation to the progressive acquisition of new data, especially epidemiologic. Among these, there is an important study of particular concern on a cohort of numerous industry workers [5] in which possible confounding factors had been appropriately controlled, which revealed a statistically significant excess of deaths due to nasopharyngeal cancer, on which IARC has basically founded its reassessment of the substance placing it in category 1. As previously discussed also in other independent studies, excess of nasopharyngeal cancer [8-13] was observed.

Differences in evaluations and classifications of carcinogenicity published by organisms and agencies involved in those duties are not uncommon and may have important implications in risk management in various countries. In general, the causes of these differences may be due to the different objectives which the organisms or agencies have (such as protection of workers, as in the case of ACGIH or of the general population as in case of WHO or the US EPA or more generally as an independent scientific reference as in case of IARC), as well as to different procedures and approaches which each may use [63]. For example, in the EU existing substances are classified by a working group (The Commission Working Group on the Classification and Labelling of Dangerous Substances) (C&L Group) composed of representatives of the Member States and of industry. The latter participate as observers. The substances to be classified are proposed by a Member State who acts as Rapporteur Country who prepares a complete and concise file, according to a standard format, containing all the available information deriving from public literature as well as from confidential data produced by Industry, and the proposed classification. In the case of formaldehyde, France acted as Rapporteur. The data are generally integrated by other Member States and by industry. In case they are available, evaluations previously formulated by internationally known organisms are taken into consideration. The group may also count on the contribution of the Working Group of Specialized Experts (The Commission Group of Specialised Experts in the Fields of Carcinogenicity, Mutagenicity, and Reprotoxicity) regarding carcinogenesis, mutagenesis and reproductive toxicity (which meets at the

request of the C&L Group and expresses opinions on specific and well documented issues, each time there is lack of agreement on classification of a particular substance or in case of particularly complex problems. This group is constituted of specialized experts of various Member States. Industry is not formally represented but may at times be invited. The names of the members of the group are officially known but the minutes of the meetings do not reveal the name of individual experts. This also ensures that experts not be subject to pressure by parties involved.

IARC takes into consideration, on its own accord, as indicated in the preface of the monographs and reconfirmed recently in the January 2006 issue [64], only papers published or in press. Reports of government agencies subjected to peer review and widely available are also taken into consideration. Exceptions can be made, in specific cases, to include reports, abstracts and theses in their final form and publicly available whenever their conclusion are considered relevant in the formulation of a final evaluation. This choice is contrary to the choices made by other national and international agencies (*i.e.* EU and Food and Agriculture Organization-WHO) and can actually lead to the exclusion of confidential scientific documentation, often of adequate quality, studies conducted in accordance with Good Laboratory Practice and in agreement with recognized guidelines proposed by industry for regulation. IARC's assumption is that the published data be screened by anonymous referees before its publication, and subsequently by the international scientific community that is somehow able to guarantee the adequacy, validity and interpretation of the study.

CCTN utilizes, to express its own opinions both published literature as well as confidential data, like the EU does.

Regarding formaldehyde it is worth noting that, even before IARC's new evaluation in 2004, the conclusions regarding the evidence of carcinogenicity emerging from epidemiologic studies were different. Both IARC (1995) [22] and the US EPA (1991) [49] considered evidence in man limited while as early as 1981 NTP considered formaldehyde a probable carcinogen in humans [29]. CCTN, though considering evidence of experimental carcinogenicity sufficient and considering the epidemiologic one not assessable, placed the substance in the category of “substances to be considered carcinogenic in man”. In 1996, when CCTN's criteria were harmonized with those of the EU, CCTN itself, though the EU had placed/assigned the substance to category 3, continued reconfirming the substance in category 2 [34, 35].

Currently, IARC's recent evaluation seems to take on a primary role, both in terms of quality of studies considered and of the level of analysis of the problem by the Agency's group of experts and has stimulated, from various organisms, first of all the EU, the revision of the substance's evaluation. It is worth mentioning that while IARC carries out, as mentioned in the preamble, a role as aid to regulatory decision-making aiming to supply information which may assist national and inter-

national authorities arrange its risk evaluation and independently formulate their own policies of regulations, in case of the EU, a classification of carcinogenicity in categories 1 and 2 has an immediate effect on regulation: it should suffice to consider that classification in category 3 currently excludes formaldehyde from the application of measures of workers' safety and protection mentioned in the Legislative Decree 66/2000 related to carcinogens in workplaces, with the consequences that this can lead to regarding prevention. In the EU, placing formaldehyde in categories 1 or 2 of carcinogenicity would lead to inclusion of the substance in the list of substances subject to directive 76/769/EEC related to restrictions in marketing and use, which among other restrictions, prohibits the presence of CMR substances in categories 1 and 2 above 0.1% in weight in products intended for sale to the general public.

DISCUSSION

The evaluation and risk management criteria for the general population (living environments) and for workers (workplaces) are notoriously different. The reasons for these differences include, for example, the different length of exposure (for the general population it is for a lifetime, 24 hours a day, every day of the year; at workplaces, instead, it is for the number of years worked, for 8 hours a day, for 5 days/week, and essentially for about 240 days/year). Furthermore, each category's vulnerability is different. The general population includes newborns, children, adolescents, the elderly, pregnant women, individuals with pathologic conditions, etc. categories not normally included in the working population, who should generally include healthy adults subject to regular medical surveillance and not particularly old.

Furthermore, there are notable differences between the criteria and the theoretical principles of each organism for the evaluation and management of carcinogenic risk. For example, regarding the general population, US EPA [50] and WHO [52, 53] have adopted the principle of the absence of thresholds, and therefore a linear relationship between risk and exposure for low doses (direct relationship), for carcinogens which act on the DNA, and anyway in absence of clear elements which justify different choices. In particular, the US EPA specifies that "linearity" for low doses (default criteria) needs to be considered in the absence of objective data which demonstrate a "non linearity", or a quicker decrease of risk as a function of exposure as opposed to what happens in a linear relation; furthermore, in some cases it proposes the definition of "carcinogenic for high doses" (which, somehow, requires the existence of a threshold), whenever this is demonstrated by experimental evidence. Such is the case of chloroform which is classified by EPA as "likely to be carcinogenic to humans by all routes of exposure" under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues and not "likely to be carcinogenic to humans by any route of exposure" under exposure conditions that do not cause cytotoxicity and cell regeneration" [65].

In any case, it is worth noting that the hypothesis of linearity for low doses suggests that the result of the risk assessment is the indication of exposure levels that can be associated to very low risk levels (1 out of 10 000, 1 out of 100 000, 1 out of 1 000 000), allowing the "decision-maker", with some flexibility, the choice of exposure level within the above levels. These or similar criteria have been adopted by some European Countries and have been considered by the EU Working Group based on evaluation of risk of new and existing substances, within the various methods of evaluation [66].

With reference to the work environment, these criteria are generally not used. Regardless of that, there are however differences in relation to the criteria and the level of caution used in evaluations. For example, NIOSH in its Pocket guide to Chemical Hazards [61] presents its limits (REL), along with those of OSHA (PEL) (generally higher), while aiming for clarity and transparency, and the differences are justified by specific criteria adopted by NIOSH. This agency's New Policy [61] calls for a more inclusive policy in relation to scientific progress and improvements in approaches for estimating and managing risk (not only for exposures which have no effects, but also for residual risks and for the minimum measurable level).

Anyway, even within the variability of evaluation, classification, evaluation criteria and risk management, the availability offered nowadays by scientific networks and the criteria used may allow reaching reasonable and shared choices.

The above can suggest a substantial variability between classifications, evaluations and risk managements adopted in different environments and by various organizations and organisms. However, in terms or practical consequences, these differences diminish. For example, the regulation of the exposure of the general population to benzene, aromatic polycyclic hydrocarbons, and fine powders in urban air is the same over the Europe, and is substantially comparable to the one adopted in the US. Relatively similar practical criteria are adopted in various countries for water quality. Differences generally emerge when new data are available and a new process of evaluation is under way. These may depend on the different rate with which various countries and agencies complete their evaluation process, and also on economic and operational consequences tied to the adoption of new limits, especially if more restrictive. For example, regarding the working environment, NIOSH in the USA, organism which is part of the National Institutes of Health (NIH), as early as 1976 recommended a 1 ppm REL (Recommended Exposure Level), TWA for 8 hours for formaldehyde, which became 0,016 ppm in 1992, TWA for 10 hours. Evidently these parameters were and are considerably lower than contemporary ones of other organisms (for example, OSHA in the USA). It is worthwhile noting that the REL, differently from PEL of the OSHA which has legal value, is a recommended level and not a standard set by an agency, issued by an agency whose duty is to furnish consultancy to the US Department of Labor

Table 1 | Limits of exposure of formaldehyde in workplaces

Year	Agency	Value	Exposure limit (ppm)
1946	ACGIH	MAC	10
1948	ACGIH	TWA	5
1963	ACGIH	Ceiling	5
1972	ACGIH	Ceiling	2
1972	OSHA		3
1976	NIOSH		1
1978	OSHA	8-hour TWA	3
1978	OSHA	Ceiling	5
1981	NIOSH		3
1985	ACGIH	8-hour TWA	1
1985	ACGIH	STEL	2
1988	OSHA	8-hour TWA	1
1988	OSHA	STEL	2
1992*	OSHA	8-hour TWA	0.75
1992*	OSHA	15-minute STEL	2
1992*	OSHA	action level	0.5
1992*	NIOSH	10-hour TWA	0.016
1992*	NIOSH	TWA- Ceiling	0.1
1992*	ACGIH	Ceiling	0.3

*currently valid value

and to its organisms, a responsibility which is independent of economic and practical aspects. Table 1 shows the temporal evolution of limits for formaldehyde in workplaces, which are currently all below 1 ppm (TWA). Finally, it is worth considering that actual average exposition is generally considerably lower than limits, and that one should adequately consider the meaning attributed by each agency to the proposed limits. For example ACGIH, upon proposing its TLV, reports that the majority of workers may remain

exposed, day by day, to TLV without negative effects on health, however, due to considerable individual variability, a small percentage of workers may report disorders due to presence of some substances whose concentrations are equal to or lower than TLV, and in an even small percentage of individuals, one may note a stronger effect of worsening of preexisting conditions or the onset of an occupational disease. Furthermore, some individuals may be hypersensitive or particularly sensitive to certain substances as a consequence of genetic factors, age, style of life, medical cures and previous exposure. Such workers may result not adequately protected from undesired effects on health due to substances present at concentrations equivalent or lower than TLV. The occupational doctor is expected to determine the degree of protection required for such individuals [56]. Generally anyway, ACGIH recommends exposure to carcinogens to be kept at the lowest levels and, in the event of workers exposed to carcinogens of category A1 with a TLV and to carcinogens of category A2 e A3, exposure must be carefully checked so as to keep it at reasonably low levels below TLV. These considerations are important to fully understand the meaning ACGH assigns to TLV.

Finally, it is worth noting that Professor Zito, in 1996, at the National Toxicological Advisory Commission made the following consideration: “formaldehyde should be correctly classified by the EU as R49 (can cause cancer by inhalation)” [35].

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Note

From the early-80's, at CCTN, Professor Zito actively collaborated in evaluating the carcinogenic role of formaldehyde identifying and exploring the most critical aspects and highlighting the importance of a precautionary and reasonable approach. In researching for data for this paper in the historical archives of the National Inventory of Chemical Substances, numerous papers authored by the professor had been carefully typed (often using a worn-out ribbon) as was his style.