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Exemptions:

WATCH COMMITTEE

The carcinogenicity of formaldehyde

Issue

1. To obtain a WATCH position on the strength of evidence that formaldehyde has caused cancer in humans.

Timing

2. Advice on this issue is sought now in preparation for an anticipated submission on the classification of formaldehyde for carcinogenicity by the relevant French authority to the European Commission's (EC's) Classification and Labelling Working Group (EC C&L WG) in Spring 2005.

Recommendation

3. That WATCH develops a position on the Action points at paragraph 22.

Background

4. It is quite some time since formaldehyde was considered in any context in the regulatory processes with which HSE and the ACTS/WATCH advisory committee structures are involved.

5. Airborne formaldehyde has long been recognised as an irritant towards the eyes, nose and respiratory tract. Human experience has shown that a single exposure to formaldehyde can cause sensory irritation when above the threshold concentration for this effect and, at sufficiently high levels, causes tissue damage in these regions. Repeated inhalation exposure can produce marked, chronic inflammation of the upper respiratory tract in experimental animals. Formaldehyde is also a direct-acting mutagen *in vitro* and has produced genetic damage at the initial site-of-contact in experimental animals.

6. These two properties of irritancy and genotoxicity raise concerns for carcinogenic potential. Long-term inhalation of formaldehyde has been shown consistently to produce malignant tumours of the nasal epithelium in rats; although interestingly, in the studies conducted thus far, a much lower tumour incidence, and in males only, has been reported in similar studies in mice using comparable exposure levels to those used in the rat studies, and no tumours have arisen in hamsters.

7. In the rat studies, nasal epithelium tumours appeared under exposure conditions which also resulted in marked, chronic inflammation of the upper respiratory tract; no tumours arose as a result of formaldehyde exposure in large groups of rats exposed to concentrations provoking no, or lesser degrees of inflammation (0.3 – 2 ppm). Such observations have led to a hypothesis that formaldehyde can produce tumours in the upper respiratory tract, at least in rats, only under conditions of chronic inflammation.

8. There have been over 50 epidemiological investigations of cancer in formaldehyde-exposed workers and these have been reviewed periodically by a range of different authorities – eg HSE (1981), IARC (1987, 1995), IPCS (1989, 2002), DECOS (2003), OECD (2002), Agency for Toxic Substances and Disease Registry (1999), EC C&L WG (19th/22nd ATP). These reviews cover the literature available up to 2000. Consistently, each has reached a similar conclusion: namely that although some individual studies are suggestive of formaldehyde having caused nasopharyngeal or nasal cancer in exposed populations, the overall strength of evidence has fallen short of showing a clear and causal association with formaldehyde exposure. Additionally, all acknowledge the biological plausibility that formaldehyde could produce cancer of the respiratory tract under circumstances of sustained cytotoxicity at the site of contact. There has been no convincing evidence for an association between formaldehyde exposure and cancer of any other sites.

9. However, a number of new epidemiology studies have been reported since 2000. Some of these provide further evidence in relation to formaldehyde exposure and cancer of the upper respiratory tract; in addition, the authors of some also raise concerns for leukaemia in humans. In 2004, IARC reappraised its position on the carcinogenic potential of formaldehyde, taking these new studies into consideration, and reached the following conclusion in relation to nasopharyngeal cancer (see Annex 1):

“Overall, the Working Group concluded that the results of the study of industrial workers in the USA, supported by the largely positive findings from other studies, provided **sufficient** epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans.”

10. This development has triggered a number of reactions, one of which is the French Competent Authority declaring its intention to put a classification proposal for formaldehyde to the EC C&L WG in Spring 2005. HSE has also received a number of enquiries about its position on the carcinogenic potential of formaldehyde. Given the importance of formaldehyde as a chemical and the significance and consequences of pronouncing a substance as a “human carcinogen”, the advice of WATCH on this matter is now sought.

Argument

11. The focus of this package is on the human epidemiological evidence for the carcinogenicity of formaldehyde. At this stage, there is no intention to publish an updated assessment of formaldehyde toxicity, and so the attached

annexes have been constructed only for the purpose of providing the basis for the WATCH discussion in relation to human cancer hazard.

12. Annex 2 provides a brief toxicological profile for formaldehyde, which helps to set the cancer findings into an overall context. This profile is based on information taken from recent reviews (e.g. by DECOS, 2002; OECD hazard assessment, 2002) and so with the exception of the carcinogenicity endpoint, has not involved any evaluation by HSE of the primary literature, beyond that done in the past in other contexts.

13. In relation to cancer, the epidemiological literature mainly relied on by the IARC Working Group in reaching its recent position on nasopharyngeal cancer has been summarised by HSE in Annex 3. It should be noted that where an evaluative conclusion has been included in these summaries, this represents the conclusion of the study authors. In addition, because these are the studies mainly relied upon by the IARC Working Group for its revised classification, on their own, they will tend over-emphasise the strength of evidence in support of a causal association, since clearly many of the studies not supporting the IARC conclusion have not been summarised in Annex 3.

14. One of the largest and most informative cohort studies is that of Hauptmann *et al* (2004). This study looks at the most recent mortality experience of a cohort of ~25 500 workers from 10 US plants (the NCI cohort). The Hauptmann study, along with earlier analyses of this NCI cohort, identifies one particular plant - the Wallingford Plant - as the source of the majority of the nasopharyngeal cancer cases. This triggered a separate analysis of the Wallingford Plant cohort, the mortality experience of which has been most recently updated by Marsh *et al* (2002).

15. Given the importance of these two cohort studies to the overall evidence base for formaldehyde exposure and nasopharyngeal cancer, the published studies by Hauptmann *et al* and Marsh *et al* are provided at Annexes 4 and 5 respectively.

16. HSE's overall interpretation of the data from the post-2000 studies is that they justify increased concern for the carcinogenic potential of formaldehyde in humans (specifically in relation to nasopharyngeal cancer), but that this falls short of providing conclusive evidence that formaldehyde exposure has caused nasopharyngeal cancer in humans; there are some inconsistencies in the findings of the most prominent new studies which lack a clear explanation.

17. In relation to the apparent association seen in some studies between formaldehyde exposure and leukaemia, based on recent reviews of the evidence, and also considering biological plausibility, HSE considers that there is no basis for any concern for this cancer.

18. To help and inform the debate at WATCH, HSE has invited Professor David Coggon of the MRC Environmental Epidemiology Unit, who was a member of the IARC Working Group for formaldehyde, to the January WATCH meeting.

Link to HSC Strategy

19. The links are that this is an **emerging issue**:

- with potential impact on HSE's statutory responsibilities in relation to C&L
- the resolution of which will be beneficial to the Cancer Sub-programme, in its attempts to identify the priority areas for action in aiming to reduce the risk and subsequent occurrence of occupational chemical-induced cancer
- relevant to the prioritisation (by ACTS) of 15 substances, including formaldehyde, currently ascribed MELs, which have been identified as requiring review when the new "WEL" OEL system comes into effect in April 2005

Consultation

20. At the time of sending to WATCH, we have also made this paper available to a small number of representatives from industry who have expressed an interest (Borden Chemicals, FIRA International Ltd, Syngenta), as well as to David Coggon.

European Context

21. We have been informed of an intention by the relevant French authority (INRS) to make a submission to the EC Classification and Labelling Working Group in Spring 2005 on the classification of formaldehyde for carcinogenicity.

Action

22. WATCH is asked to consider this paper and to:

- i. construct a description of what it feels is the strength of evidence for formaldehyde having caused cancer in humans; and
- ii. set this into context with the available experimental animal data on carcinogenicity and the overall toxicological profile for formaldehyde

Contact:

Nicola Gregg
WATCH Secretariat

References / Attachments

Annex 1 – IARC summary of data reported and evaluation for formaldehyde

Annex 2 – Toxicological profile for formaldehyde

Annex 3 – A study-by-study summary of the human epidemiological data mainly relied upon by the IARC Working Group in reaching its conclusion in relation to formaldehyde exposure and nasopharyngeal cancer.

Annex 4 – Hauptmann M, JH Lubin, PA Stewart, RB Hayes and A Blair (2004). Mortality from solid cancers among workers in formaldehyde industries. *American Journal of Epidemiology* **159**: 1117-1130.

Annex 5 - Marsh GM, AO Youk, JM Buchanich, LD Cassidy, LJ Lucas, NA Esmen and IM Gathuru (2002). Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde. *Toxicology and Industrial Health* **18**: 257-268.