UPPER AIRWAYS CANCER, MYELOID LEUKAEMIA AND OTHER CANCERS IN A COHORT OF BRITISH CHEMICAL WORKERS EXPOSED TO FORMALDEHYDE

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Abstract

The International Agency for Research on Cancer controversially has classified formaldehyde as causing nasopharyngeal carcinoma and myeloid leukaemia. To provide further information on this question, we extended follow-up of 14,008 chemical workers at six factories in England and Wales, covering the period 1941-2012. Mortality was compared with national death rates, and associations with incident upper airways cancer and leukaemia were explored in nested case-control analyses. Excess deaths were observed from cancers of the oesophagus (100 v 93.1 expected), stomach (182 v 141.4), rectum (107 v 86.8), liver (35 v 26.9) and lung (813 v 645.8), but none of these tumours exhibited a clear exposure-response relationship. Nested case-control analyses of 115 men with upper airways cancer (including one nasopharyngeal cancer), 92 with leukaemia, and 45 with myeloid leukaemia indicated no elevations of risk in the highest exposure category (high exposure for 1 year). When the two highest exposure categories were combined the odds ratio for myeloid leukaemia was 1.26 (95% confidence interval: 0.39, 4.08). Our results provide no support for a hazard of myeloid leukaemia, nasopharyngeal carcinoma or other upper airways tumours from formaldehyde, and indicate that any excess risk of these cancers, even from relatively high exposures, is at most small.

Keywords

Cancer; chemical industry; formaldehyde; mortality; myeloid leukaemia; nasopharyngeal cancer

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Formaldehyde is a major industrial chemical, total annual production in the USA and Western Europe exceeding 10 million tonnes [1]. Resins derived from formaldehyde are used to make adhesives and binders (e.g. for manufacture of particle board, paper and vitreous synthetic fibres), plastics and coatings, and in textile finishing [2]. In addition,

formaldehyde is an intermediate in the production of various other chemicals, and in aqueous solution (formalin) it is used as a disinfectant and preservative. As well as the exposures that arise from its manufacture and use, it is encountered as a product of combustion (e.g. in vehicle exhausts and tobacco smoke) [2]. Moreover, it is formed endogenously in humans, for example from metabolism of the methanol that occurs naturally in fruit [3].

In 2006, the International Agency for Research on Cancer classified formaldehyde as a human carcinogen [1]. This decision was based on evidence that it was cytotoxic, genotoxic, caused nasal cancer in rats when inhaled at high concentrations, and was associated with an increased risk of nasopharyngeal cancer in epidemiological studies. The association with nasopharyngeal cancer was not entirely consistent, but was apparent in a cohort study conducted by the US National Cancer Institute (NCI) of factories that made formaldehyde or products containing formaldehyde [4]; in analyses of proportional mortality among US embalmers [5] and at Danish companies manufacturing or using formaldehyde [6]; and in a number of case-control studies [7-11].

A hazard of nasopharyngeal cancer is plausible insofar as the nasopharynx is a site of direct contact with inhaled formaldehyde. More controversial is the possibility that formaldehyde might also cause leukaemia. Suspicion of such an effect was raised by an elevated risk of myeloid leukaemia associated with high peak exposures in the NCI cohort study [12], an observation that was supported by increased risks also in a cohort of garment manufacturers [13] and in earlier studies of embalmers, pathologists and anatomists [14-19]. On the other hand, a large study of workers heavily exposed to formaldehyde in the British chemical industry had found no excess of leukaemia, although it did not examine risks for myeloid leukaemia specifically [20].

In 2006, the International Agency for Research on Cancer did not consider the evidence sufficient to be confident that formaldehyde causes leukaemia in humans [1], but that position was revised in 2012, by which time the NCI study had been extended [21], and an association had been observed also in a nested case-control study of workers in the funeral industry [22]. Although most of the International Agency for Research on Cancer monograph panel judged that the evidence for a hazard of leukaemia was now sufficient, it remains uncertain how inhaled formaldehyde might reach haematopoietic stem cells at sufficient concentrations to induce malignancy, and others have argued that the evidence is unconvincing [23-24].

Whether or not formaldehyde causes leukaemia is an important question, because if it acts systemically and not only at anatomical sites which are directly exposed, there are implications for the risk assessment of other chemicals for which it is a product of metabolism. For example, the carcinogenicity of formaldehyde was recently raised as a concern in a risk assessment for the artificial sweetener, aspartame, since aspartame is metabolised to formaldehyde via methanol [25].

To provide further information on the risks of cancer from formaldehyde, we updated follow-up of the British cohort of chemical workers [20] by 12 years, with special focus on upper airways cancer and leukaemia.

MATERIALS AND METHODS

The cohort was originally established in the early 1980s [20, 26-27], and comprised men who had been employed at six chemical factories in England and Wales at a time when formaldehyde was produced or used, and for which employment records were thought to be complete (Table 1). At five factories, all male employees were enrolled, while at the sixth (British Petroleum), where only a small proportion of the workforce had been exposed to formaldehyde, recruitment was limited to formaldehyde workers and a subset of men who had worked in other parts of the plant (two for each exposed man).

Subjects were identified from personnel records, and information was abstracted on name, date of birth and job history while at the factory. An occupational hygienist then classified job titles according to their exposure to formaldehyde (background, low, moderate, high or unknown). Measurements of formaldehyde were not available from before 1970, but from later measurements and workers' recall of irritant symptoms, it was estimated that background exposure corresponded to time-weighted concentrations of <0.1 ppm; low exposure to 0.1-0.5 ppm; moderate exposure to 0.6-2.0 ppm and high exposure to > 2.0 ppm. Within each factory, each job title was assigned the same exposure category across all time periods, but the same job title was not necessarily classed to the same exposure category at different factories.

Other substances handled at some of the factories included styrene, ethylene oxide, epichlorhydrin, asbestos, chromium salts, cadmium and various organic solvents, but any exposures to these agents would generally have been relatively low.

The cohort was traced through the National Health Service Central Register (now the Health and Social Care Information Centre), and in some cases national insurance records, and followed to 31 December 2012. For men who had died, we obtained the underlying and contributing causes of death, coded to the ninth (deaths up to the end of 2000) or tenth (deaths since 2000) revisions of the International Classification of Diseases. For those with registered cancers, we obtained the type of cancer and date of registration.

Statistical analysis

Statistical analysis was carried out with Stata v 13 software (StataCorp. College Station, TX).

We used the person-years method to compare the mortality of cohort members with that of the national population of England and Wales, according to categories of exposure. These analyses were based on underlying cause of death, and reference rates were for five-year age bands and calendar periods (except for deaths during 2010-2012, for which rates during 2005-2012 were used). Each man was considered at risk from the latest of: a) 1 January 1941, b) the date from which employment records at the factory were believed to be

complete, and c) the date when he entered the relevant exposure category. He then remained at risk until the earliest of: a) exiting the relevant exposure category, b) death, c) loss to follow-up for other reasons (e.g. emigration), and d) 31 December 2012. Men who could not be traced at the Health and Social Care Information Centre or in national insurance records were deemed lost to follow-up at their last known date of employment. Standardised mortality ratios (SMRs) were derived as the ratios of observed to expected deaths, with 95% confidence intervals based on the Poisson distribution. Person-years analyses were carried out for major groupings of causes of death and for specific cancers, with codes in relevant revisions of the International Classification of Diseases as set out in Web Table 1. For selected causes of death, mortality by exposure was additionally examined by Poisson regression, with the log of the expected number of deaths as the offset.

Risks for upper airways cancer (tumours of the lip, tongue, mouth, nose and nasal sinuses, pharynx and larynx) and leukaemia were then explored further in nested case-control analyses. For each outcome, we identified all men for whom the diagnosis was recorded as an underlying or contributing cause of death, or as a cancer registration. The date of diagnosis was taken as the first date at which the diagnosis was known to have been made. Each case was individually matched with up to 10 controls who: a) did not have the relevant diagnosis during the study period, b) worked at the same factory as the case, c) were alive and under follow-up when the case was diagnosed, and d) were born within two years of the case. This was achieved through an algorithm designed to ensure that the same control was not assigned to more than one case in the same diagnostic category (upper airways cancer or leukaemia) and to minimise the number of cases with only a small number of controls. Where more than 10 possible controls were available for the same case, we gave preference to those with closer dates of birth. Associations with level and duration of exposure to formaldehyde (at a time point defined for each matched set as five years before the date when the case was first known to have been diagnosed) were assessed by conditional logistic regression, and summarised by odds ratios.

Ethical approval

Ethical approval was originally provided by the British Medical Association Ethics Committee, and later reaffirmed by the National Research Ethics Service Committee South Central - Portsmouth.

RESULTS

The number of men included in the analysis (14,008) differed slightly from that in the last reported follow-up of the cohort (14,014) [20]. Seventeen subjects from the previous analysis were excluded because they were found to be female (15) or had incorrect dates in their employment histories that had to be re-classified as unknown (2). This loss was partially offset by inclusion of 11 men who had been omitted from the earlier analysis - one previously thought to be female, and 10 for whom dates in the employment history had been treated as missing, but which could reasonably be imputed.

A total of 9,172 cohort members had exposures above background, including 3,991 who at some time were highly exposed. Most of the latter (86%) were at the British Industrial Plastics factory (Table 1).

Within the total cohort of 14,008 men, 7,378 were known to have died by the end of the follow-up period (2,188 of the deaths occurring since the last published analysis of mortality [20]), 5,449 were still alive, and the other 1,181 had been lost to follow-up at an earlier stage. The last group included 171 men who could not be traced through the Health and Social Care Information Centre or social security records beyond their last known date of employment, and were followed only to that date.

Overall mortality in the cohort was significantly higher than expected from national rates (SMR 1.05, 95% confidence interval: 1.03, 1.08), as was that from all cancers (SMR 1.10), respiratory disease (SMR 1.13) and digestive disease (SMR 1.22) (Table 2). In addition, there was a non-significant excess of deaths from injury and poisoning (SMR 1.10), whereas mortality from circulatory diseases was close to expectation (SMR 0.99). The elevation in total mortality was attributable to high death rates at three factories (British Industrial Plastics, and the Synthite facilities at Mold and West Bromwich), while at Ciba Geigy, overall mortality was significantly lower than expected (SMR 0.81). When the analysis was broken down by highest lifetime level of exposure, risk of death increased with exposure for all causes, all cancers, circulatory disease, respiratory disease and digestive diseases, but not for injury and poisoning (Table 2).

The main contribution to the elevated mortality from cancer came from tumours of the oesophagus (100 deaths v 93.1 expected), stomach (182 v 141.4), rectum (107 v 86.8), liver (35 v 26.9) and lung (813 v 645.8), and for each of these tumours, SMRs were even higher among men who had experienced high exposure (SMRs 1.33 to 1.59) (Table 3 and Web Table 2). When findings were broken down by factory, there was no excess of deaths from any of these tumours at Ciba Geigy, but increased rates of lung cancer were observed at each of the other five factories, of cancers of the stomach, rectum and liver at four factories, and of oesophageal cancer at three (data not shown). Among men with high exposure, mortality was also increased for most categories of upper airways cancer (lip 2 deaths v 0.2 expected, tongue 3 v 2.1, mouth 3 v 1.9, pharynx 6 v 4.1, nose and nasal sinuses 0 v 0.9, larynx 11 v 5.6, total 25 v 14.8). However, there was no excess mortality from nasopharyngeal cancer specifically, the only death occurring in a man with low/moderate exposure (1.7 deaths expected for exposures above background). For myeloid leukaemia, there were 36 deaths overall as compared with 29.9 expected, but there was no elevation of mortality among men with high exposure (SMR 0.93).

Table 4 breaks down mortality by duration of high exposure for those cancers with more than 25 deaths in the high exposure category. None of the seven tumours exhibited a clear exposure-response relationship. In particular, mortality from cancers of the oesophagus, pancreas and lung was highest in men whose high exposure was for less than one year.

Table 5 shows risks of death from lung cancer and respiratory disease by highest level of exposure, as estimated by Poisson regression with adjustment for factory.

For both causes of death, risk was lower in men with prolonged high exposure than in those highly exposed for less than one year. Furthermore, this pattern persisted when each man's first 35 years of follow-up were disregarded.

The nested case-control analyses focused on 115 men with upper airways cancer and 92 with leukaemia, including 45 with myeloid leukaemia. Most were first identified from cancer registrations, including a substantial proportion who subsequently died with the cancer as an underlying or (more rarely) contributing cause (Web Table 3). For six men with upper airways cancers, the site of cancer recorded on the death certificate differed from that which had been registered. The most common sites of upper airways cancer were the larynx (53 cases), pharynx (28 cases, including one cancer of the nasopharynx), mouth (14 cases) and tongue (9 cases).

We were able to find a total of 1138 controls for the 115 men with upper airways cancer, and 914 for the 92 with leukaemia, including 450 for the 45 with myeloid leukaemia. Four cases had fewer than 10 controls (two, five, six and nine).

Table 6 summarises the relation of upper airways cancer and leukaemia to the highest category of exposure that had been achieved by five years before the case was diagnosed. No significant associations were observed, and odds ratios for the highest category of exposure (high exposure for 1 year) were less than or close to one for each of cancer of the larynx, cancer of the mouth, cancer of the pharynx, cancer of the tongue, all upper airways cancer, myeloid leukaemia and all leukaemia. When the two highest exposure categories were combined (i.e. all high exposure), the odds ratio for myeloid leukaemia was 1.26 (95% confidence interval: 0.39, 4.08). Repeat analysis using a lag of two rather than five years gave similar results.

DISCUSSION

Our study provides no evidence that formaldehyde poses a hazard either of upper airways cancer or of myeloid leukaemia. Total mortality in the cohort was elevated, as was that from various more specific causes, but the pattern of results suggests that this was attributable to non-occupational confounding factors and not an adverse effect of formaldehyde.

Our analysis adds substantially to the last published results from the same cohort [20], with inclusion of more than 2000 additional deaths. Furthermore, through nested case-control studies, we were able to use data on cases ascertained from cancer registrations as well as death certificates. This not only enhanced statistical power, but also gave greater assurance of diagnostic accuracy. We did not attempt independent histological review of cases, but it seems unlikely that diagnostic errors would have caused us seriously to underestimate risks. We did not carry out a person-years analysis based on cancer registrations because historically the completeness of cancer registration in England and Wales varied by region, and national registration rates therefore would not have provided a reliable reference.

Only limited data were available on levels of formaldehyde in the workplaces studied, precluding the derivation of quantitative metrics of cumulative and peak exposure. However, we are confident that our high exposure category corresponded to average concentrations in

the order of 2 ppm or higher, and the absence of increased cancer risks among men with prolonged exposures at this level is reassuring.

We did not attempt to update job histories beyond the early 1980s when the cohort was first assembled. However, by that time, relatively few cohort members (<5%) were still employed at the participating factories, and exposures were lower than in earlier years.

The elevation of total mortality in the cohort resulted largely from high death rates at three of the six participating factories (British Industrial Plastics, and the Synthite plants at Mold and West Bromwich), and was most marked in men with high exposure. Causes of death that contributed importantly to the excess included cancers of the oesophagus, stomach, rectum, liver and lung, and respiratory and digestive disease. In addition, mortality from circulatory disease was increased among men with high exposure. It seems likely, however, that these findings are explained by non-occupational factors. Most of the diseases contributing to the high overall mortality are associated with socio-economic deprivation, and also occurred at high rates in the general population of the areas surrounding the Synthite and West Bromwich factories [20]. In contrast, at Ciba-Geigy, which was located in a more prosperous and less industrialised area, total mortality was significantly lower than expected. Furthermore, analyses for cancers of the oesophagus, stomach, rectum and lung showed no clear exposure-response relationship for duration of high exposure to formaldehyde (Table 4). And Poisson regression indicated that mortality from lung cancer and respiratory disease was highest in men with high exposure for less than one year, and close to expectation in those with high exposure for 15 years (Table 5). That this pattern persisted when the first 35 years of each man's follow-up was disregarded suggests that it is not attributable to healthy worker selection.

Two other large cohort studies have examined patterns of mortality among formaldehyde workers in manufacturing industry. In the most recent follow-up of the NCI cohort, there was a slightly increased risk of deaths from all causes among exposed workers (SMR 1.03), but mortality was lower in the highest category of cumulative exposure [28]. Similarly, although there was an overall excess of lung cancer (SMR 1.20), risk declined significantly with increasing cumulative exposure, while deaths from circulatory and respiratory disease were close to expectation and there was a non-significant deficit of deaths from liver cancer.

In the other study, which followed up more than 11,000 garment manufacturers in Georgia and Pennsylvania, mortality from all causes, all cancers and lung cancer was similar to that expected from national rates, and an overall excess of deaths from chronic obstructive pulmonary disease (SMR 1.16), did not extend to workers with the longest duration of exposure [29].

When the results from our study are set alongside these findings, there is little to suggest that formaldehyde increases the risk of any of the most common causes of death.

Nasopharyngeal cancer is rare in western populations, and only one death from this disease was recorded in our cohort as compared with 1.7 expected in men with more than background exposure. However, there was a suggestion of increased mortality from other upper airways cancers among men with high exposures to formaldehyde. We therefore

undertook a nested case-control study of upper airways cancers (lip, tongue, mouth, pharynx and larynx, but not salivary glands), which along with the nasopharynx, have the greatest potential for direct contact with inhaled formaldehyde.

A further justification for considering these cancers as a group was that within the upper airways, distinguishing the exact site of origin of a tumour is not always straightforward. This may explain why some cases had different upper airways cancers recorded on death certificates from those which had been registered during life. By combining all upper airways cancers, and ascertaining cases from cancer registrations as well as death certificates, we were able to base our analysis on 115 cases - substantially more than the 56 deaths from these tumours in the person-years analysis of mortality. However, no relation was found with level of exposure to formaldehyde, either for upper airways cancers collectively, or for cancers at specific sites in the upper airways (Table 6).

In person-years analyses, mortality from myeloid leukaemia was a little higher than expected (36 deaths observed v 29.9 expected), but there was no increased risk among men with high exposure (SMR 0.93). Nor did the nested case-control analysis, which included an additional nine cases, give any indication of a hazard, and there was no association with leukaemia more broadly.

Although risk of myeloid leukaemia was higher among members of the NCI cohort with higher peak exposures to formaldehyde, there was no overall excess of the disease in exposed workers, and no relation to cumulative exposure [21]. Similarly, a case-control study of deaths among a population of embalmers found higher risk of myeloid leukaemia with increasing duration of embalming [22], but with no increase in proportional mortality for the cohort as a whole. And in the other major cohort study of an industrial population exposed to formaldehyde, risk of myeloid leukaemia was increased in people employed as garment workers for 10 years or longer (SMR 1.84), but not to the point of statistical significance [29]. In the context of this relatively weak epidemiological evidence, our results call into question the International Agency for Research on Cancer's classification of formaldehyde as a cause of myeloid leukaemia.

In summary, while our results do not exclude the possibility that formaldehyde causes myeloid leukaemia, nasopharyngeal carcinoma or other upper airways tumours, they provide no support for excess risks of these cancers. Furthermore, they indicate that if such hazards do exist, then the absolute risks, even from relatively high exposures, are at most small.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

NCI   National Cancer Institute

SMR   Standardised mortality ratio

REFERENCES

1. International Agency for Research on Cancer (IARC). Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. Vol. 88. IARC; Lyon (France): 2006. IARC monographs on the evaluation of carcinogenic risks to humans

2. International Agency for Research on Cancer (IARC). Chemical agents and related occupations. Vol. 100F. IARC; Lyon (France): 2012. IARC monographs on the evaluation of carcinogenic risks to humans

3. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. [Accessed February 13, 2014] COT statement on the effects of chronic dietary exposure to methanol. http://cot.food.gov.uk/pdfs/cotstatementmethanol201102revjuly.pdf Published 2011. Updated August 1, 2011

4. Hauptmann M, Lubin JH, Stewart PA, et al. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol. 2004; 159(12):1117–1130. [PubMed: 15191929]

5. Hayes RB, Blair A, Stewart PA, et al. Mortality of U.S. embalmers and funeral directors. Am J Ind Med. 1990; 18(6):641–652.

6. Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control. 1995; 6(4):354–360. [PubMed: 7548723]

7. Vaughan TL, Strader C, Davis S, Daling JR. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int J Cancer. 1986; 38(5):685–688. [PubMed: 3770996]

8. Roush GC, Walrath J, Stayner LT, et al. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. J Natl Cancer Inst. 1987; 79(6):1221–1224. [PubMed: 3480373]

9. West S, Hildesheim A, Dosemeci M. Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. Int J Cancer. 1993; 55(5):722–727. [PubMed: 7503957]

10. Vaughan TL, Stewart PA, Teschke K, et al. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. Occup Environ Med. 2000; 57(6):376–384. [PubMed: 10810126]

11. Hildesheim A, Dosemeci M, Chan CC, et al. Occupational exposure to wood, formaldehyde, and solvents and risk of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2001; 10(11):1145–1153. [PubMed: 11700262]

12. Hauptmann M, Lubin J, Stewart P, Hayes R, Blair A. Mortality from lymphohematopietic malignancies among workers in formaldehyde industries. J Natl Cancer Inst. 2003; 95(21):1615–1623. [PubMed: 14600094]

13. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ med. 2004; 61(3):193–200. [PubMed: 14985513]

14. Walrath J, Fraumeni JF Jr. Mortality patterns among embalmers. Int J Cancer. 1983; 31(4):407–411. [PubMed: 6832852]

15. Walrath J, Fraumeni JF Jr. Cancer and other causes of death among embalmers. Cancer Res. 1984; 44(10):4638–4641. [PubMed: 6467219]

16. Levine RJ, Andjelkovich DA, Shaw LK. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. J Occup Med. 1984; 26(10):740–746. [PubMed: 6491780]

17. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. J Natl Cancer Inst. 1986; 77(6):1217–1224. [PubMed: 3467114]

18. Hayes RB, Blair A, Stewart PA, et al. Mortality of U.S. embalmers and funeral directors. Am J Ind Med. 1990; 18(6):641–652. [PubMed: 2264563]

19. Hall A, Harrington JM, Aw TC. Mortality study of British pathologists. Am J Ind Med. 1991; 20(1):83–89. [PubMed: 1867220]

20. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J Natl Cancer Inst. 2003; 95(21):1608–1615. [PubMed: 14600093]

21. Beane Freeman LE, Blair A, Lubin JH, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst. 2009; 101(10):751–761. [PubMed: 19436030]

22. Hauptmann M, Stewart PA, Lubin JH, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009; 101(24): 1696–1708. [PubMed: 19933446]

23. Checkoway H, Boffetta P, Mundt DJ, Mundt KA. Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and the risk of leukemia and other lymphohematopoietic malignancies. Cancer Causes Control. 2012; 23(11):1747–1766. [PubMed: 22983399]

24. Cole P, Adami H-O, Trichopoulos D, Mandel J. Formaldehyde and lymphohematopoietic cancers: a review of two recent studies. Reg Toxicol Pharmacol. 2010; 58(2):161–166.

25. European Food Safety Authority. Output of technical report on the draft EFSA scientific opinion on the re-evaluation of aspartame (E951) as a food additive. European Food Safety Authority; 2013. Published 2013 [Accessed February 13, 2014]

26. Acheson ED, Barnes HR, Gardner MY, Osmond C, Pannett B, Taylor CP. Formaldehyde in the British chemical industry. An occupational cohort study. Lancet. 1984; 1(8377):611–616. [PubMed: 6142316]

27. Gardner MJ, Pannett B, Winter PD, Cruddas AM. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br J Ind Med. 1993; 50(9):827–834. [PubMed: 8398877]

28. Beane Freeman LE, Blair A, Lubin JH, Steart PA, Hayes RB, Hoover RN, Hauptmann M. Mortality from solid tumors among workers in formaldehyde industries: an update from the NCI cohort. Am J Indust Med. 2013; 56(9):1015–1026.

29. Meyers AR, Pinkerton LE, Hein MJ. Cohort mortality study of garment industry workers exposed to formaldehyde: update and internal comparisons. Am J Indust Med. 2013; 56(9):1027–1039.

Table 1

Distribution of Cohort by Company: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

Company	Location	Year formaldehyde first used	Year from which personnel records were complete	Activities	No. in Cohort	No. in cohort with high exposure[a]
Borden	North Baddesley, Hampshire	About 1955	1958	Production of formaldehyde and use on site for manufacture of resins and adhesives	1908	51
Synthite	West Bromwich, West Midlands	1920s	1950	Production of formaldehyde as formalin, paraformaldehyde, and alcoforms	756	259
Synthite	Mold, Clwyd, Wales	1950	1951	Production of formaldehyde as formalin, paraformaldehyde, and alcoforms	459	105
British Industrial Plastics	Oldbury, West Midlands	1937	1938	Production of formaldehyde and use on site for manufacture of resins and adhesives	4790	3417
Ciba-Geigy	Duxford, Cambridgeshire	1937	1957	Production of formaldehyde and use on site for manufacture of resins and adhesives	2619	159
British Petroleum	Barry, South Glamorgan, Wales	1948	1948	Production of resins from imported formalin	3476	0

[a] High level of exposure to formaldehyde estimated as greater than 2 ppm

Table 2

Mortality by Cause and Highest Level of Exposure: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

Cause of death	Highest Level of Exposure[a]	Observed	Expected	SMR	95% CI
All cancers [b]	Background	660	678.1	0.97	0.90, 1.05
	Low/Moderate	771	722.9	1.07	0.99, 1.14
	High	810	631.2	1.28	1.20, 1.37
	All Subjects	2241	2032.2	1.10	1.06, 1.15
Circulatory disease [c]	Background	910	986.9	0.92	0.86, 0.98
	Low/Moderate	1032	1062.0	0.97	0.91, 1.03
	High	1072	999.6	1.07	1.01, 1.14
	All Subjects	3014	3048.5	0.99	0.95, 1.02
Respiratory disease [d]	Background	257	280.1	0.92	0.81, 1.04
	Low/Moderate	321	302.1	1.06	0.95, 1.19
	High	396	282.9	1.40	1.27, 1.54
	All Subjects	974	865.2	1.13	1.06, 1.20
Digestive diseases [e]	Background	84	80.2	1.05	0.84, 1.30
	Low/Moderate	104	85.5	1.22	0.99, 1.47
	High	100	70.8	1.41	1.15, 1.72
	All Subjects	288	236.5	1.22	1.08, 1.37
Injury and poisoning [f]	Background	104	90.5	1.15	0.94, 1.39
	Low/Moderate	115	95.0	1.21	1.00, 1.45
	High	69	75.5	0.91	0.71, 1.16
	All Subjects	288	261.0	1.10	0.98, 1.24
All Causes	Background	2209	2302.4	0.96	0.92, 1.00
	Low/Moderate	2529	2468.1	1.02	0.99, 1.07
	High	2640	2236.3	1.18	1.14, 1.23
	All Subjects	7378	7006.8	1.05	1.03, 1.08

CI = confidence interval

SMR = standardised mortality ratio

ICD = International Classification of Diseases

[a] At each time during follow-up, subjects were classed according to the highest grade of exposure experienced up to that date.

[b] ICD9 140-208; ICD10 C00-C97

[c] ICD9 390-459; ICD10 I00-I99

[d] ICD9 460-519; ICD10 J00-J99

[e] ICD9 008-009, 520-579; ICD10 K00-K93

[f] ICD9 800-999; ICD10 U509, V01-Y89

Table 3

Mortality from Selected Cancers by Highest Level of Exposure: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

Cancer	Highest Level of Exposure[a]	Observed	Expected	SMR	95% CI
Lip	Background	0	0.2	0.00	0.00, 21.04
	Low/Moderate	0	0.2	0.00	0.00, 19.25
	High	2	0.2	9.98	1.21, 36.04
	All Subjects	2	0.6	3.52	0.43, 12.73
Tongue	Background	1	2.5	0.40	0.01, 2.25
	Low/Moderate	2	2.6	0.76	0.09, 2.75
	High	3	2.1	1.43	0.30, 4.18
	All Subjects	6	7.2	0.83	0.31, 1.81
Mouth [b]	Background	4	2.2	1.81	0.49, 4.62
	Low/Moderate	0	2.3	0.00	0.00, 1.58
	High	3	1.9	1.58	0.33, 4.62
	All Subjects	7	6.5	1.08	0.44, 2.23
Pharynx [b]	Background	6	4.9	1.23	0.45, 2.67
	Low/Moderate	5	5.1	0.97	0.32, 2.27
	High	6	4.1	1.47	0.54, 3.20
	All Subjects	17	14.1	1.20	0.70, 1.93
Oesophagus	Background	30	32.2	0.93	0.63, 1.33
	Low/Moderate	31	34.0	0.91	0.62, 1.29
	High	39	26.9	1.45	1.03, 1.98
	All Subjects	100	93.1	1.07	0.87, 1.31
Stomach	Background	51	45.1	1.13	0.84, 1.49
	Low/Moderate	59	48.6	1.21	0.92, 1.57
	High	72	47.8	1.51	1.18, 1.90
	All Subjects	182	141.4	1.29	1.11, 1.49
Large Intestine	Background	36	44.2	0.81	0.57, 1.13
	Low/Moderate	40	47.1	0.85	0.61, 1.16
	High	50	41.1	1.22	0.90, 1.60
	All Subjects	126	132.4	0.95	0.79, 1.13
Rectum	Background	36	28.9	1.25	0.87, 1.72
	Low/Moderate	35	30.8	1.14	0.79, 1.58
	High	36	27.0	1.33	0.93, 1.84
	All Subjects	107	86.8	1.23	1.01, 1.49
Liver [c]	Background	13	9.5	1.36	0.73, 2.33
	Low/Moderate	11	10.0	1.10	0.55, 1.97
	High	11	7.4	1.49	0.75, 2.67
	All Subjects	35	26.9	1.30	0.91, 1.81
Pancreas	Background	29	29.5	0.98	0.66, 1.41
	Low/Moderate	34	31.3	1.09	0.75, 1.52

Cancer	Highest Level of Exposure[a]	Observed	Expected	SMR	95% CI
	High	28	26.7	1.05	0.70, 1.52
	All Subjects	91	87.4	1.04	0.84, 1.28
	Background	1	0.9	1.08	0.03, 6.01
Nose and nasal sinuses	Low/Moderate	1	1.0	1.01	0.03, 5.62
	High	0	0.9	0.00	0.00, 4.03
	All Subjects	2	2.8	0.71	0.09, 2.55
	Background	2	6.0	0.33	0.04, 1.20
Larynx	Low/Moderate	9	6.4	1.40	0.64, 2.66
	High	11	5.6	1.96	0.98, 3.50
	All Subjects	22	18.1	1.22	0.76, 1.84
	Background	218	210.5	1.04	0.90, 1.18
Lung	Low/Moderate	262	225.8	1.16	1.02, 1.31
	High	333	209.5	1.59	1.42, 1.77
	All Subjects	813	645.8	1.26	1.17, 1.35
	Background	38	61.1	0.62	0.44, 0.85
Prostate	Low/Moderate	64	65.5	0.98	0.75, 1.25
	High	45	56.2	0.80	0.58, 1.07
	All Subjects	147	182.9	0.80	0.68, 0.94
	Background	35	25.4	1.38	0.96, 1.91
Bladder[b]	Low/Moderate	26	27.2	0.96	0.62, 1.40
	High	25	24.4	1.02	0.66, 1.51
	All Subjects	86	77.1	1.12	0.89, 1.38
	Background	13	15.3	0.85	0.45, 1.45
Kidney[b]	Low/Moderate	19	16.1	1.18	0.71, 1.84
	High	18	12.9	1.40	0.83, 2.21
	All Subjects	50	44.3	1.13	0.84, 1.49
	Background	21	17.1	1.23	0.76, 1.87
Brain and nervous system	Low/Moderate	16	18.0	0.89	0.51, 1.45
	High	8	14.2	0.56	0.24, 1.11
	All Subjects	45	49.3	0.91	0.67, 1.22
	Background	21	17.4	1.21	0.75, 1.84
Non-Hodgkin lymphoma[b]	Low/Moderate	19	18.3	1.04	0.62, 1.62
	High	13	14.4	0.90	0.48, 1.55
	All Subjects	53	50.1	1.06	0.79, 1.38
	Background	3	9.6	0.31	0.06, 0.91
Multiple myeloma[b]	Low/Moderate	15	10.2	1.47	0.82, 2.43
	High	10	8.4	1.18	0.57, 2.18
	All Subjects	28	28.2	0.99	0.66, 1.43
	Background	17	18.1	0.94	0.55, 1.51
Leukaemia	Low/Moderate	24	19.1	1.26	0.81, 1.87
	High	13	15.8	0.82	0.44, 1.41
	All Subjects	54	53.0	1.02	0.77, 1.33

Cancer	Highest Level of Exposure[a]	Observed	Expected	SMR	95% CI
Myeloid leukaemia [b]	Background	12	10.4	1.16	0.60, 2.02
	Low/Moderate	16	10.9	1.46	0.84, 2.38
	High	8	8.6	0.93	0.40, 1.82
	All Subjects	36	29.9	1.20	0.84, 1.66

CI = confidence interval SMR = standardised mortality ratio

[a] At each time during follow-up, subjects were classed according to the highest grade of exposure experienced up to that date

[b] Because of changes in disease classification, the earliest follow-up for these cancers was from 1950

[c] Because of changes in disease classification, the earliest follow-up for these cancers was from 1958

Table 4

Mortality from Selected Cancers by Duration of High Exposure: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

Cancer	<1 year			Duration of high exposure[a] 1-14 years				15 years			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
Oesophagus	21	12.2	1.72	1.07, 2.64	13	10.8	1.21	0.64, 2.06	4	3.7	1.09	0.30, 2.79
Stomach	30	19.7	1.52	1.03, 2.18	31	19.9	1.56	1.06, 2.21	11	7.5	1.47	0.73, 2.63
Large intestine	25	17.8	1.40	0.91, 2.07	18	16.6	1.09	0.64, 1.72	7	6.2	1.14	0.46, 2.34
Rectum	13	11.7	1.12	0.59, 1.91	16	11.0	1.45	0.83, 2.36	5	4.0	1.25	0.40, 2.91
Pancreas	14	11.7	1.20	0.65, 2.01	11	10.8	1.02	0.51, 1.82	3	3.8	0.79	0.16, 2.30
Lung	157	89.4	1.76	1.49, 2.05	131	85.6	1.53	1.28, 1.82	42	31.6	1.33	0.96, 1.79
Prostate	13	24.2	0.54	0.29, 0.92	25	21.7	1.15	0.74, 1.70	7	9.7	0.72	0.29, 1.49

CI = confidence interval SMR = standardised mortality ratio

[a] Duration of high exposure was unknown for 43 men with high exposure

Table 5

Mortality from lung cancer and respiratory disease by highest level of exposure: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

a) Analysis based on each worker's entire period of follow-up

Highest level of exposure	Cancer of lung			Respiratory disease		
	Deaths	RR	95%CI	Deaths	RR	95%CI
Background	218	1		257	1	
Low/moderate	262	1.15	0.95, 1.40	321	1.14	0.95, 1.36
High <1 year	157	1.59	1.21, 2.09	187	1.37	1.07, 1.75
High 1–14 years	131	1.41	1.07, 1.86	149	1.14	0.89, 1.47
High 15 years	42	1.21	0.83, 1.76	51	0.89	0.63, 1.24

b) Analysis excluding each worker's first 35 years of follow-up

Highest level of exposure	Cancer of lung			Respiratory disease		
	Deaths	RR	95%CI	Deaths	RR	95%CI
Background	103	1		146	1	
Low/moderate	107	1.06	0.79, 1.42	167	1.13	0.89, 1.44
High <1 year	59	1.42	0.92, 2.18	97	1.40	1.00, 1.97
High 1–14 years	45	1.39	0.89, 2.18	81	1.45	1.02, 2.05
High 15 years	21	1.15	0.67, 1.99	26	0.71	0.44, 1.14

CI = confidence interval RR = Risk ratio

Table 6

Associations of Selected Cancers with Exposure to Formaldehyde in Nested Case-control Analyses: Study of British Chemical Workers Exposed to Formaldehyde 1941-2012

Cancer	Highest Level of Exposure	Cases	Controls	OR[a]	95% CI
Upper airways	Background	37	349		
	Low/Moderate	33	384	0.84	0.49, 1.42
	High <1 year	25	204	1.28	0.61, 2.67
	High 1 year	20	201	1.03	0.48, 2.18
Cancer of the Larynx	Background	14	156		
	Low/Moderate	17	177	1.20	0.53, 2.73
	High <1 year	14	104	2.02	0.65, 6.27
	High 1 year	8	93	1.30	0.39, 4.38
Cancer of the Mouth	Background	5	44		
	Low/Moderate	3	44	0.59	0.12, 2.98
	High <1 year	3	30	0.97	0.13, 7.47
	High 1 year	3	22	1.38	0.17, 11.1
Cancer of the Pharynx	Background	10	89		
	Low/Moderate	9	95	0.81	0.30, 2.22
	High <1 year	3	35	0.63	0.13, 3.03
	High 1 year	6	53	0.81	0.22, 3.05
Cancer of the Tongue	Background	5	34		
	Low/Moderate	2	26	0.41	0.06, 2.58
	High <1 year	1	19	0.19	0.01, 2.58
	High 1 year	1	11	0.34	0.03, 4.35
All Leukaemia	Background	35	349		
	Low/Moderate	39	350	1.08	0.64, 1.84
	High <1 year	9	87	0.84	0.32, 2.20
	High 1 year	9	128	0.59	0.23, 1.50
Myeloid leukaemia	Background	17	180		
	Low/Moderate	19	186	1.10	0.51, 2.38
	High <1 year	5	34	1.77	0.45, 7.03
	High 1 year	4	50	0.96	0.24, 3.82

CI = confidence interval OR = odds ratio

[a] All risk estimates are relative to background exposure, and relate to exposure status five years before the case (for controls, the matched case) was first known to have been diagnosed.