

**This is a draft paper for discussion. It should not be quoted, cited or reproduced.**

**CC/05/6**

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,  
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**SINGLE/SHORT TERM EXPOSURE TO CARCINOGENS**

**COVERING PAPER**

1. A short overview of the evidence for single exposure carcinogens was provided as part of the horizon scanning exercise for 2004. (Annex 1). This provided information on definitions of single and short duration exposures and the identification of single exposure carcinogens. An overview of one paper suggested an approach to risk assessment using dose-rate scaling factors for amending the virtually safe dose estimate. Members agreed that the review of single/short term exposure carcinogens should be given a high priority.
2. The DH Toxicology Unit has drafted an initial short discussion paper which focuses on the evidence for carcinogenesis in humans following short term exposures to chemicals (<1 year). (Annex 2). What are members views regarding this evidence?
3. A copy of the Calabrese and Blain paper (Toxicological Sciences, 50, 169-185, 1999) is appended as Annex 3. This paper formed part of the basis for the initial scanning review presented in 2004. What are members views regarding the proposal presented by Calabrese and Blain that single exposure/short term exposure carcinogenesis is possibly a generic feature of carcinogens? Is the phenomenon likely to be restricted to a subset of possibly high potency genotoxic carcinogens?
4. Do members have any other comments on the information reviewed by Calabrese and Blain?
5. A further paper will be drafted for a future meeting which will attempt to consider possible approaches to risk assessment.

**Secretariat March 2004**

**This is a draft paper for discussion. It should not be quoted, cited or reproduced.**

**Potential short-exposure human carcinogens: – an overview of studies relating to limited-exposure occupational carcinogens cited by Calabrese & Blain (1999).**

COC/04/32 section 4 (Single Exposure Carcinogens) indicated a paper by (Calabrese and Blain, 1999), which described the construction of a database of “single-exposure” chemical and physical agents associated with tumour development (in the absence of exogenous promotional stimuli) in animal models. Single-exposure in this case was defined as a situation in which the agent was administered only once, with no additional treatment, and where tumours were examined as an endpoint. In addition to this database of single-exposure experimental carcinogens, the authors cited a small number of agents which had been identified by literature searches as limited-exposure (< 1 year) occupational carcinogens in humans. The agents cited were benzene, beryllium, vinyl chloride, aromatic amines of benzidine, and arsenic. The following report contains a summary of the studies identified by (Calabrese and Blain, 1999), and any additional studies identified by literature search for short-exposure carcinogenicity of these agents.

**Benzene**

*Background*

IARC classification

Benzene is classified by IARC as a group I carcinogen, on the basis of sufficient evidence for carcinogenicity in humans and animals (International Agency for Research on Cancer, 1987).

Experimental data

Oral administration of benzene to rats and mice induced neoplasms at multiple sites. Inhalation in mice produced a tendency towards induction of lymphoid neoplasms. Exposure of rats by inhalation increased the incidence of neoplasms, mainly carcinomas, at various sites. In a mouse-lung tumour bioassay by intraperitoneal injection, an increase in the incidence of lung adenomas was observed in males. Occupational exposure to benzene has been associated with chromosomal aberrations in peripheral lymphocytes. Benzene has shown some positive clastogenic effects, mutation and cell transformation in experimental studies in rodent and human cells, but was not mutagenic to bacteria (International Agency for Research on Cancer, 1987).

Cancer epidemiology

Case and cohort studies have shown increased incidence of leukaemias associated with occupational exposure to benzene (International Agency for Research on Cancer, 1987). A retrospective cohort study in China revealed an SMR of 574 ( $p < 0.01$ ) for association leukaemia associated with benzene exposure (30 cases in test cohort of ~ 28 000 workers exposed to benzene vv. 4 in a reference cohort of ~ 28 000 workers in

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

machine production, textile and cloth factories (Yin et al., 1987). Mean concentrations of benzene were in the range of 10 – 1000 mg/m<sup>3</sup> (mostly in the range of 50-500 mg/m<sup>3</sup>).

### Studies reporting short-term exposure

]

(Bond et al., 1986) reported an evaluation of mortality in a total of 956 workers with a history of exposure to benzene. A total of 265 of these workers had estimated exposure durations < 1 year. A significant excess of deaths from skin cancer was observed (O/E = 4/1.0), but the authors determined that this was unlikely to be linked to benzene exposure. A non-significant excess of deaths from leukaemia, in particular myeloblastic leukaemia, was noted (O/E = 4/2.1), the shortest estimated duration for benzene exposure amongst these individuals was 1.5 years (range to 23 years). However, the authors identified a potential for brief, but potentially relatively high, exposures to benzene (as high as 937 ppm in some work areas).

## **Beryllium**

### IARC classification

Beryllium and beryllium compounds are classified by IARC as Group 1 carcinogens (carcinogenic to humans), on the basis of sufficient evidence for carcinogenicity in humans and experimental animals (International Agency for Research on Cancer, 1993).

### Experimental data

Experimental studies have shown dose-related increase in lung tumours (mostly adenocarcinomas and adenomas) in rats exposed to beryllium metal and beryllium compounds by inhalation or single intratracheal instillation. Rabbits given intravenous injections or bone-implantations of beryllium metal or various beryllium compounds developed osteosarcomas (International Agency for Research on Cancer, 1993).

Beryllium compounds are not mutagenic in most bacterial systems. Other genotoxicity studies of beryllium compounds have shown mixed results, with some studies showing evidence for clastogenic effects in mammalian cells *in vitro* (International Agency for Research on Cancer, 1993).

Increased lung beryllium levels may persist for very long periods (eg up to 20 years) in exposed subjects. Beryllium exposure in humans is associated with acute (fatal) pneumonitis and, after long-term exposure, with chronic, non-caseating granulomatous pulmonary disease with a high rate of fatality. Similar disease is seen in exposed animals. Beryllium also causes contact dermatitis and associated, cell-mediated immunological reactions.

### Cancer epidemiology

Early cohort mortality studies showed a low, but significant association between occupational exposure to beryllium and increase in deaths from lung cancer in

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

workers in the US. Risks for lung cancer were consistently higher in facilities where excess mortality from nonmalignant respiratory disease occurred. Excess mortality appears to have been reduced by the introduction of measures to reduce exposure in the 1950s. Recent follow-up of workers on the US Beryllium Case Registry (workers registered with acute or chronic beryllium-related respiratory disease) also showed excess mortality from lung cancer, which was greater in those with acute than chronic disease (International Agency for Research on Cancer, 1993).

### Studies reporting short-term exposure

(Monson, 1980) presented data on deaths due to lung cancer and to non-neoplastic respiratory disease (NNRD) according to years of exposure and years since onset of exposure in beryllium workers. Excess lung cancer mortality occurred with a latency of  $\geq 15$  years, and was seen mainly in men exposed for  $< 5$  y (O/E = 40/28.6), and to a lesser extent in those with longer exposure (O/E = 7/5.7). Excess mortality due to NNRD was confined to men with shorter exposures (O/E = 29/15.6 for  $< 5$  y exposure, 2/3.2 for 5+ y exposure). Exposure concentrations were not described, but regarding dose-response the authors noted that “If years of exposure to a beryllium factory can be taken as a rough measure of dose, there is an inverse relationship between exposure and excess disease... However, many of the short-term workers probably had the highest acute exposures to beryllium.”

(Mancuso, 1980) evaluated lung cancer mortality in a cohort of 3685 men employed, pre-1950, in beryllium manufacturing industries, as compared with that of a control group of workers employed in the viscose rayon industry. A significant excess of lung cancer mortality was seen in the beryllium workers (O = 80, E = 57 or 50<sup>1</sup>, SMR = 140 or 158<sup>1</sup>). Breakdown by duration of employment (Table 1) also showed an excess of lung cancer specifically in the  $\leq 12$  m group (O = 52, E = 37 or 31<sup>1</sup>, SMR = 138 or 164<sup>1</sup>). Analysis of lung tissue from 2 of these cases (described as employed for 2 quarters and 7 quarters of a year, respectively) at a time greater than 20 years after last exposure showed elevated beryllium content in both cases. The authors noted that deposition and retention of beryllium in the lungs for many years increases the medical concern pertaining to the carcinogenic potential of beryllium in the tissues of exposed subjects. They also noted that this conclusion is supported by the findings of animal experiments demonstrating the development of metaplasia and lung cancer following a single intratracheal installation of beryllium. They concluded that “it is reasonable to believe that the amount of exposure to beryllium to establish a biological effective dose for the induction of lung cancer occur within a few months of exposure regardless of whether the individual is employed for less than 1 year or employed for 10 years. The additional amount of exposure to beryllium may not be required, once the biological effective carcinogenic dose has occurred in a worker”.

(Wagoner et al., 1980) expanded the cohort mortality study of (Mancuso, 1980) to include workers employed during a later time-period (to 1967<sup>2</sup>). This study also showed increased SMRs from lung cancer in occupationally-exposed men, however there was no pattern of increasing or decreasing SMR with duration of employment.

---

<sup>1</sup> Depending on criteria for categorisation of viscose rayon workers

<sup>2</sup> Note, in 1949 a standard of 2  $\mu\text{g}/\text{m}^3$  beryllium exposure was introduced

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

A study of mortality patterns in men enrolled in the Beryllium Case Registry<sup>3</sup> during the period 1952-1975 (as compared with those of the general US [male] population) showed that increased risk of lung cancer mortality was confined to men classified with acute, as opposed to chronic, respiratory illness<sup>4</sup> (at the time of entry into the case registry) (Infante et al., 1980). However, the numbers involved were small; of a total of 421 men in the registry (139 dead at point of evaluation), there were 6 deaths from lung cancer in the acute group (O/E = 6/1.91; SMR = 314) and 1 in the chronic group (O/E = 1/1.38; SMR = 72). The majority of excess deaths (total mortality, O/E = 139/66; SMR = 211) was accounted for by NNRD (O/E = 52/3.17; SMR = 1640). The authors noted that there was an excess of lung cancer deaths in men with acute, but not chronic respiratory disease, however this may be due to the very high number of deaths from NNRD in the chronic respiratory disease group (O/E = 42/0.65). Of the 6 deaths from lung cancer in the acute group, exposure times to beryllium were estimated as < 5 y (n = 1); ~ 6 m (n = 1); 2 m (n = 1); < 1 m (n = 3).

Further follow-up of the Beryllium Case Registry was reported by (Steenland and Ward, 1991) (follow-up to 1988, now including women). An excess for lung cancer was noted (SMR = 2.00; 95% CI, 1.33-2.89), and again this was greater among cohort members with acute beryllium pneumonitis (SMR = 2.32; 95% CI, 1.35-3.72) than those with chronic beryllium disease (SMR = 1.57; 95% CI, 0.75-2.89). However, no substantial variation in SMR was seen with duration of exposure.

### **Vinyl Chloride**

#### IARC classification

Vinyl chloride (VC) is classed as a Group 1 carcinogen (carcinogenic to humans) on the basis of sufficient evidence in humans and animals (International Agency for Research on Cancer, 1987).

#### Experimental data

VC has been shown to produce tumours (mammary gland, lung, Zymbal gland and skin, and angiosarcomas of the liver) in mice, rats and hamsters, by oral or inhalation exposure routes. The mode of action is well-elucidated: VC is metabolised to a reactive metabolite, which interacts with DNA, forming DNA adducts, ultimately leading to tumour formation (International Agency for Research on Cancer, 1987; EPA, 2000).

#### Cancer epidemiology

---

<sup>3</sup> The (US) Beryllium Case Registry was established in 1952 to collect data on the epidemiology, diagnosis, clinical features, course and complications of beryllium-related diseases. Individuals who were entered into the Registry were categorised as having either acute beryllium-induced pneumonitis or chronic systemic beryllium diseases.

<sup>4</sup> Chronic beryllium disease results from hypersensitivity to beryllium and may occur at much lower exposures than acute beryllium pneumonitis (International Agency for Research on Cancer, 1993).

## **This is a draft paper for discussion. It should not be quoted, cited or reproduced.**

In humans a causal relationship has been established in a large number of epidemiological studies between exposure to vinyl chloride monomer (VCM) and angiosarcoma of the liver (ASL). VC exposure has also been associated with causation of other cancers (hepatocellular carcinoma, brain tumours, lung tumours, malignancies of the lymphatic and haematopoietic system) (International Agency for Research on Cancer, 1987).

### Studies reporting short-term exposure

Although (Calabrese and Blain, 1999) cited VC as implicated in cancer causation in epidemiological studies by exposure duration < 1 year, no reports were identified during the preparation of this paper. However, studies which have specifically mentioned short-term exposure durations are detailed below.

(Weber et al., 1981) examined mortality patterns in 7021 VC workers in Germany and Austria, as compared with the general population. Increased risk of death due to liver cancer (12 observed vs 0.79 expected) and some other cancers was observed. Breakdown by duration of exposure showed no deaths due to liver cancer, or increased SMR for other cancers, in the < 12 month group, although the SMR for liver tumours was significantly increased in the 13-16 month exposure group (SMR = 874), with further increases for longer exposures.

(Jones et al., 1988) reported that 11/780 deaths in 5498 men with occupational VC exposure in the UK were due to “nonsecondary liver cancer”, 7 of which were angiosarcoma. Breakdown by length of exposure to VC showed no deaths in the ≤ 1 year exposure group (however, entry criteria for the study was “completion of 1 year of employment in such an occupation”).

In a cohort of 3232 VC-exposed workers in the Soviet Union, there was a significantly increased risk of lymphomas and leukaemias in workers with the highest level of exposure (> 300 mg/m<sup>3</sup>). Breakdown by exposure level and duration of employment showed slight, non-significant increases in SMRs for deaths due to cancer in men with high and medium (30-300mg/m<sup>3</sup>) level exposures of various durations, including the 0-4 year exposure duration group. SMRs for cancer deaths in women with the highest level exposure were significantly increased in all but the 0-4 year duration group) (Smulevich et al., 1988).

(Pirastu et al., 1990) reported that 14/63 deaths in men with occupational exposure to VC in Italy were from primary liver cancer (7 angiosarcoma, 2 hepatocellular carcinoma, 5 unspecified [but thought not to be angiosarcoma]). Some men had exposures of 1 year, but these were not in the primary liver cancer group (minimum exposure 2 years).

### **Benzidine, 1-naphthylamine and 2-naphthylamine**

#### IARC classification

Benzidine and 2- (β-) naphthylamine are classified by IARC as Group 1 carcinogens (carcinogenic to humans), on the basis of sufficient evidence for carcinogenicity in

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

humans and in animals. 1- ( $\alpha$ -) naphthylamine is classified as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans, inadequate evidence for carcinogenicity in humans and animals) (International Agency for Research on Cancer, 1987).

### Experimental data

Experimental studies showed that benzidine and 2-naphthylamine produced tumours at multiple sites (including bladder tumours) in animal species, by oral administration. Benzidine also produced tumours by several other exposure routes. 1-naphthylamine showed either no carcinogenic effect, or inconclusive results, when tested in various animal species (International Agency for Research on Cancer, 1987).

Benzidine, 1- and 2-naphthylamine were mutagenic to bacteria. Benzidine and 2-naphthylamine were positive in DNA damage assays, and showed some clastogenic effects and cell transformation *in vitro* and/or *in vivo* (International Agency for Research on Cancer, 1987).

### Cancer epidemiology

Several epidemiological studies have shown that occupational exposures to benzidine and 1- and 2-naphthylamine are causally associated with an increased risk of bladder cancer (it is suggested that the association of 1-naphthylamine with bladder cancer may be a consequence of contamination with 2-naphthylamine) (International Agency for Research on Cancer, 1987).

### Studies reporting short-term exposure

(Case et al., 1954) reported that exposures of less than one year to benzidine, 2-naphthylamine or mixtures of benzidine, 1- and 2-naphthylamine were associated with increased risk of bladder cancer.

This report described an evaluation of bladder cancer incidence/deaths in men working in the British chemical industry in the first half of the twentieth century (pre-1900 to ~ 1952), noting that occupational exposures to aniline, benzidine, 1-naphthylamine and 2-naphthylamine were associated with increased risk of death from bladder cancer, and also of earlier age of onset and death from bladder cancer as compared with the general population.

A total of 455 cases of bladder cancer were identified within men “in the British chemical industry”. Of these, 311 of these men were reported as having had contact with aniline, benzidine, 1-naphthylamine or 2-naphthylamine (298 cases had contact with benzidine, 1-naphthylamine, 2-naphthylamine), and 262 of these 311 cases were on a “nominal role”<sup>5</sup> of men reported by participating firms as having had contact with these substances. Amongst the 262 cases on the nominal role (144 of whom were dead), bladder cancer was mentioned on the death certificate of 127 men, whilst it was

---

<sup>5</sup> A criteria for inclusion on the nominal roll was employment within the chemical industry for  $\leq 6$  months.

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

calculated that the expected number of deaths from bladder cancer in a group of this size within the general population would be 3-5. Hence, employment of  $\geq 6$  months in the chemical industry with exposure (but not necessarily for total employment period) to the chemicals of interest was associated with an  $\sim 30$ -fold increased risk of death from bladder cancer as compared with that in the general population.

Sub-division by chemical showed that the greatest risks were associated with exposure to 2-naphthylamine and benzidine. In addition to increased risk of death, a risk of dying of bladder cancer at an earlier age than that expected was also identified, with the average age at onset of tumour probably around 20 years earlier than that for men in the general population.

A consistent induction period of  $\sim 15$ -20 years from first contact with chemical of interest to onset of tumour was noted, ie, the earlier the age at exposure, the earlier the age of onset of tumour. However, it was noted that the induction time did not appear to be a function of dose (measured as exposure period, or severity of exposure by correlation with job type).

In this analysis, a table expressing an evaluation of the possible relationship between exposure time and induction time showed that 7 men (from a total of 281 men for whom exposure time was indicated) were exposed to benzidine, 1-naphthylamine, 2-naphthylamine or a mixture of these substances for a period of  $< 1$  year. The authors went on to calculate the "mean effective exposure" (the length of time necessary for a particular class of exposure to produce the average risk for that class of exposure). In the case of both benzidine and mixed exposures, mean effective exposure times were reached by 1 year (Figure 1). In the case of benzidine, 2-naphthylamine and mixed exposures the authors noted that "exposures of less than one year... have already produced sufficient effect to make it impracticable to attempt to obviate the risk solely by reducing the employment time".

Recently, investigators at the US National Institute for Occupational Safety (NIOSH) updated studies of bladder cancer incidence and mortality at a synthetic dye plant that manufactured 2-naphthylamine from 1940-1979. A total of 1287 men were evaluated, 87% of whom were followed for  $\geq 20$  years following first employment. Short-term workers comprised the majority of the cohort (50% employed for  $< 2$  months, 82% employed for  $< 1$  year). Cause of death analysis showed 3 cases of bladder cancer as the underlying cause of death (O/E = 3/1.3; SMR = 2.39; 95% CI, 0.49-6.99), in all 3 cases exposure duration (as duration of employment) was  $\leq 3$  months. Bladder cancer was listed on the death certificates of 8 subjects (SMR based on multiple cause referent rates = 5.63; 95% CI, 2.43-11.10), and the multiple cause SMR for bladder cancer for workers employed  $< 10$  years (the authors state that all employees in this category were actually employed  $< 1$  year) was 3.7 (95% CI, 1.21-8.68) (Axtell et al., 1998).

### **Arsenic**

#### IARC Classification

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Arsenic and arsenic compounds are classed by IARC as carcinogenic to humans (Group 1), on the basis of sufficient evidence in humans and limited evidence in experimental studies (International Agency for Research on Cancer, 1987).

### Experimental studies

The following summary of carcinogenicity studies of arsenic and arsenic compounds in animals is reproduced from the most-recent IARC update:-

“Various arsenic compounds have been tested for carcinogenicity by perinatal treatment of mice, by intratracheal instillation in hamsters and rats and by implantation into the stomach of rats. Arsenic trioxide produced lung adenomas in mice after perinatal treatment, and induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters after its intratracheal instillation. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats. A high incidence of lung carcinomas was induced in rats following a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into hamsters resulted in a borderline increase in the incidence of lung adenomas, while no such effect was observed with arsenic trisulphide. Sodium arsenite enhanced the incidence of renal tumours induced in rats by intraperitoneal injection of *N*-nitrosodiethylamine.” (International Agency for Research on Cancer, 1987).

Some studies have shown increases in clastogenic effects in humans exposed to arsenic compounds, but these results were judged to be uncertain because of methodological problems. Trivalent and pentavalent arsenic have shown some clastogenic effects *in vivo* and/or *in vitro*, but did not induce mutation in bacteria (International Agency for Research on Cancer, 1987).

### Cancer epidemiology

#### *Arsenic medications*

Reports have described an association between exposure to arsenic *via* medical treatments (eg, Fowler’s solution) and cases of skin cancer, alone or in combination with other cancers (liver angiosarcoma, intestinal and bladder cancers and meningioma). Medicinal exposure to arsenic has also been associated with liver angiosarcomas. One report described skin cancer in combination with liver angiosarcoma occurring in a 45 year old man, 33 years after short-term medicinal arsenic ingestion (6 months treatment, total intake 0.24 g arsenic) (Roat et al., 1982). Epidemiological studies have shown an excess of skin cancers, but not other cancers, associated with medical treatment with arsenic (International Agency for Research on Cancer, 1987).

#### *Environmental exposure*

Environmental exposure to arsenic through drinking water has been associated with skin cancer, and possibly other cancers (bladder, kidney, skin, lung, liver, colon). A

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

possible association of air pollution containing arsenic with lung cancer has been reported (International Agency for Research on Cancer, 1987).

### *Occupational exposure*

A dose-related, increased incidence of lung cancer has been reported in smelter workers heavily exposed to inorganic arsenic. Possible associations with other cancers (gastrointestinal, renal, haematolymphatic malignancies) were also identified. Risk of lung cancer decreases after cessation of exposure to arsenic. Work in some other occupations with arsenic exposure (but also exposure to other carcinogenic substances) has also been associated with increased incidences of cancers including lung cancer (hat makers), stomach cancer (glass blowers), skin and lung cancers (vineyard workers), lung cancer, malignant neoplasms of the lymphatic and haematopoietic tissues, and liver angiosarcomas (exposure to arsenical pesticides) (International Agency for Research on Cancer, 1987).

### Studies reporting short-term exposure

(Ott et al., 1974) examined mortality outcomes of men exposed to arsenic compounds (calcium and lead arsenate) through their work in an insecticide production unit (US), and who died in the period 1940-1972 ( $n \sim 2000$ , 173 of whom were considered to have been in jobs with exposure to arsenic compounds). Proportionate mortality analysis revealed an excess of deaths due to respiratory malignancies ( $n_{\text{exposed}} = 28$  [16.2%],  $n_{\text{controls}} = 104$  [5.7%]), and also lymphatic and haematopoietic tissue cancers ( $n_{\text{exposed}} = 6$  [3.5%],  $n_{\text{controls}} = 25$  [1.4%]). The association of respiratory malignancy death with level (TWA x duration) of arsenic exposure showed a positive dose-response. Of the 173 men who had been in arsenic-exposed jobs, 138 had worked in the exposure area for < 1 year, and of these deaths, 16 [11.6%] were due to respiratory cancer (ie, 16/28 respiratory cancer deaths in the exposed group were exposed for < 1 year).

### Reference List

Axtell,C.D., Ward,E.M., McCabe,G.P., Schulte,P.A., Stern,F.B., and Glickman,L.T. (1998). Underlying and multiple cause mortality in a cohort of workers exposed to aromatic amines. *Am. J. Ind. Med.* 34, 506-511.

Bond,G.G., McLaren,E.A., Baldwin,C.L., and Cook,R.R. (1986). An update of mortality among chemical workers exposed to benzene. *Br. J. Ind. Med.* 43, 685-691.

Calabrese,E.J. and Blain,R.B. (1999). The Single Exposure Carcinogen Database: assessing the circumstances under which a single exposure to a carcinogen can cause cancer. *Toxicol. Sci.* 50, 169-185.

Case,R.A., Hosker,M.E., McDonald,D.B., and Pearson,J.T. (1954). Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the british chemical industry. *Brit. J. Industr. Med.* 11, 75-96.

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

EPA (2000). Toxicological Review of Vinyl Chloride: In support of summary information on the integrated risk information system (IRIS). <http://www.epa.gov/iris>. U. S. Environmental Protection Agency, Washington, DC.

Infante,P.F., Wagoner,J.K., and Sprince,N.L. (1980). Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. *Environ. Res.* *21*, 35-43.

International Agency for Research on Cancer (1987). IARC monographs on the evaluation of carcinogenic risks to humans. Supplement 7: Overall evaluations of carcinogenicity: and updating of IARC Monographs Volumes 1 to 42.

International Agency for Research on Cancer (1993). IARC monographs on the evaluation of carcinogenic risks to humans. Volume 58: Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry.

Jones,R.D., Smith,D.M., and Thomas,P.G. (1988). A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. *Scand. J. Work Environ. Health* *14*, 153-160.

Mancuso,T.F. (1980). Mortality study of beryllium industry workers' occupational lung cancer. *Environ. Res.* *21*, 48-55.

Monson,R.R. (1980). *Occupational Epidemiology*. CRC Press, Boca Raton).

Ott,M.G., Holder,B.B., and Gordon,H.L. (1974). Respiratory cancer and occupational exposure to arsenicals. *Arch. Environ. Health* *29*, 250-255.

Pirastu,R., Comba,P., Reggiani,A., Foa,V., Masina,A., and Maltoni,C. (1990). Mortality from liver disease among Italian vinyl chloride monomer/polyvinyl chloride manufacturers. *Am. J. Ind. Med.* *17*, 155-161.

Roat,J.W., Wald,A., Mendelow,H., and Pataki,K.I. (1982). Hepatic angiosarcoma associated with short-term arsenic ingestion. *Am. J. Med.* *73*, 933-936.

Smulevich,V.B., Fedotova,I.V., and Filatova,V.S. (1988). Increasing evidence of the rise of cancer in workers exposed to vinylchloride. *Br. J. Ind. Med.* *45*, 93-97.

Steenland,K. and Ward,E. (1991). Lung cancer incidence among patients with beryllium disease: a cohort mortality study. *J. Natl. Cancer Inst.* *83*, 1380-1385.

Wagoner,J.K., Infante,P.F., and Bayliss,D.L. (1980). Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. *Environ. Res.* *21*, 15-34.

Weber,H., Reinl,W., and Greiser,E. (1981). German investigations on morbidity and mortality of workers exposed to vinyl chloride. *Environ. Health Perspect.* *41*, 95-99.

Yin,S.N., Li,G.L., Tain,F.D., Fu,Z.I., Jin,C., Chen,Y.J., Luo,S.J., Ye,P.Z., Zhang,J.Z., Wang,G.C., and . (1987). Leukaemia in benzene workers: a retrospective cohort study. *Br. J. Ind. Med.* *44*, 124-128.

This is a draft paper for discussion. It should not be quoted, cited or reproduced.