

## APPENDIX

### DESCRIPTIVE EVALUATIONS OF THE ANIMAL AND HUMAN EVIDENCE FOR CARCINOGENICITY OF THE CHEMICALS CONSIDERED

#### 1. ACRYLONITRILE (Group 2B)

Acrylonitrile is carcinogenic in rats after oral administration and inhalation, producing cancers of the brain, forestomach, and Zymbal gland<sup>1</sup>.

The one available study suggests 4- to 6-fold increases in the rates of lung and colon cancer in men observed for 20 or more years; however it is limited by the absence of information on smoking and on exposure to other chemicals, and by incompleteness of follow-up<sup>1</sup>.

#### 2. AFLATOXINS (Group 2A)

Aflatoxins are carcinogenic in mice, rats, fish, ducks, marmosets, tree shrews and monkeys by several routes of administration (including oral), producing mainly cancers of the liver, colon and kidney<sup>2</sup>.

Epidemiological studies have shown a positive correlation between the average dietary concentrations of aflatoxins in populations and the incidence of primary liver cancer. These studies were undertaken to test this specific hypothesis; however, no studies have been carried out which could link an increased risk of liver cancer to actual aflatoxin intake in individuals<sup>2</sup>.

---

<sup>1</sup> IARC Monographs, 19: 73-133, 1979.

<sup>2</sup> IARC Monographs, 10: 51-72, 1976.

### 3. 4-AMINOBIIPHENYL (Group 1)

4-Aminobiphenyl is carcinogenic in mice, rats, rabbits and dogs after oral administration, producing principally cancer of the urinary bladder<sup>1</sup>.

Epidemiological studies, which are confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, show a high incidence of bladder cancer<sup>1,2</sup>.

### 4. AMITROLE (AMINOTRIAZOLE) (Group 2B)

Amitrole is carcinogenic in mice and rats, producing thyroid and liver tumours following oral or subcutaneous administration<sup>3,4</sup>.

Railroad workers who were exposed to amitrole and other herbicides showed a slight (but statistically significant) excess of cancer when all sites were considered together. Because the workers were exposed to several different herbicides however, no conclusions could be made regarding the carcinogenicity of amitrole alone<sup>3</sup>.

### 5. ARSENIC AND CERTAIN ARSENIC COMPOUNDS (Group 1)

Information on the carcinogenicity of arsenic compounds in experimental animals was considered inadequate for evaluation<sup>5</sup>.

Skin cancer in humans is causally associated with exposure to inorganic arsenic compounds in drugs, drinking water and the occupational environment. The risk of lung cancer was increased 4 to 12 times in certain smelter workers who inhaled high levels of arsenic trioxide<sup>5-7</sup>.

---

<sup>1</sup> IARC Monographs, 1: 74-79, 1972.

<sup>2</sup> Melamed, M.R. (1972) Diagnostic cytology of urinary tract carcinoma. *Eur. J. Cancer*, 8: 287-292.

<sup>3</sup> IARC Monographs, 7: 31-43, 1974.

<sup>4</sup> Tsuda, H., Hananouchi, M., Tatematsu, M., Hirose, M., Hirao, K., Takahashi, M. & Ito, N. (1976) Tumorigenic effect of 3-amino-1H-1,2,4-triazole on rat thyroid. *J. Natl Cancer Inst.*, 57: 861-864.

<sup>5</sup> IARC Monographs, 2: 48-73, 1973.

<sup>6</sup> Kuratsune, M., Tokudome, S., Shirakusa, T., Yoshida, M., Tokumitsu, Y., Hayano, T. & Seita, M. (1974) Occupational lung cancer among copper smelters. *Int. J. Cancer*, 13: 552-558.

<sup>7</sup> Tokudome, S. & Kuratsune, M. (1976) A cohort study on mortality from cancer and other causes among workers at a metal refinery. *Int. J. Cancer*, 17: 310-317.

However, the influence of other constituents of the working environment cannot be excluded in these studies. Case reports have suggested an association between exposure to arsenic compounds and blood dyscrasias and liver tumours<sup>1-4</sup>.

## 6. ASBESTOS (Group 1)

All types of commercial asbestos fibres that have been tested are carcinogenic in mice, rats, hamsters and rabbits, producing mesotheliomas and lung carcinomas after inhalation, and after intrapleural, intratracheal and intraperitoneal administration<sup>5</sup>.

Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high incidence of lung cancer. A predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile asbestos. Gastrointestinal tract cancers were increased in groups exposed occupationally to amosite, chrysotile or mixed fibres containing crocidolite. An excess of cancer of the larynx was also observed in exposed workers. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and crocidolite mines, and in persons living with asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibres increase lung cancer incidence independently. When present together, they act multiplicatively<sup>5</sup>.

- 
- <sup>1</sup> Kjeldsberg, C.R. & Ward, H.P. (1972) Leukemia in arsenic poisoning. *Ann. Intern. Med.*, 77: 935-937.
  - <sup>2</sup> Kyle, R.A. & Pease, G.L. (1965) Hematologic aspects of arsenic intoxication. *N. Engl. J. Med.*, 273: 18-23.
  - <sup>3</sup> Brady, J., Liberatore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J.N.P., Bishop, M., Polan, A. & Vianna, N. (1977) Angiosarcoma of the liver: an epidemiologic survey. *J. Natl Cancer Inst.*, 59: 1383-1385.
  - <sup>4</sup> Lander, J.J., Stanley, R.J., Sumner, H.W., Boswell, D.C. & Aach, R.D. (1975) Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). *Gastroenterology*, 68: 1582-1586.
  - <sup>5</sup> IARC Monographs, 14: 1-106, 1977.

## 7. AURAMINE (Group 2B) and

## 8. THE MANUFACTURE OF AURAMINE (Group 1)

Commercial auramine is carcinogenic in mice and rats after oral administration, producing liver tumours, and after subcutaneous injection in rats, producing local sarcomas<sup>1</sup>.

The manufacture of auramine (which also involves exposure to other chemicals) has been shown in one study to be causally associated with an increase in bladder cancer. The actual carcinogenic compound(s) has not been specified precisely<sup>1</sup>.

## 9. BENZENE (Group 1)

Benzene has shown no evidence of carcinogenicity when tested in mice by skin application. Other animal experiments were considered to be inadequate to evaluate the carcinogenicity of benzene<sup>2,3,4</sup>.

Several case reports as well as an epidemiological case control study suggest a relationship between benzene exposure and leukaemia<sup>2</sup>. Two cohort studies<sup>5,6</sup> showed an increased incidence of acute non-lymphocytic leukaemia in workers exposed to benzene. There has been an additional report of a large number of leukaemia cases (most of which were acute non-lymphocytic) among a group of workers exposed to benzene<sup>7,8</sup>.

---

<sup>1</sup> IARC Monographs, 1: 69-73, 1972.

<sup>2</sup> IARC Monographs, 7: 203-221, 1974.

<sup>3</sup> Maltoni, C. & Scarnato, C. (1977) Le prime prove sperimentali dell'azione cancerogena del benzene. *Gli Ospedali della Vita*, 4: 111-113.

<sup>4</sup> Ward, J.M., Weisburger, J.H., Yamamoto, R.S., Benjamin, T., Brown, C.A. & Weisburger, E.K. (1975) Long-term effect of benzene in C57BL/6N mice. *Arch. Environ. Health*, 30: 22-25.

<sup>5</sup> Infante, P.F., Wagoner, J.K., Rinsky, R.A. & Young, R.J. (1977) Leukaemia in benzene workers. *Lancet*, ii: 76-78.

<sup>6</sup> Ott, M.G., Townsend, J.C., Fishbeck, W.A. & Langner, R.A. (1978) Mortality among individuals occupationally exposed to benzene. *Arch. Environ. Health*, 33: 3-10.

<sup>7</sup> Aksoy, M. & Erdem, S. (1978) Followup study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. *Blood*, 52: 285-292.

<sup>8</sup> Aksoy, M., Erdem, S. & Dinçol, G. (1974) Leukemia in shoe-workers exposed chronically to benzene. *Blood*, 44: 837-841.

## 10. BENZIDINE (Group 1)

Benzidine is carcinogenic in experimental animals after oral and subcutaneous administration, producing liver tumours in rats and hamsters, and bladder cancers in dogs<sup>1</sup>.

Case reports and follow-up studies of workers provide sufficient evidence that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer<sup>1</sup>. The causal association is strengthened by data which suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure<sup>2</sup>.

## 11. BERYLLIUM AND CERTAIN BERYLLIUM COMPOUNDS (Group 2B)

Inhalation of beryllium sulphate, beryl ore, and bertrandite produce lung tumours in rats. Beryllium oxide and beryllium sulphate produce lung tumours in monkeys after intrabronchial implantation or inhalation. Zinc beryllium silicate, beryllium metal, and beryllium phosphate all produce bone tumours in rabbits following intravenous injection<sup>3</sup>.

Five early epidemiological studies were considered inadequate to evaluate the carcinogenic effects of beryllium. Three recent epidemiological studies<sup>4-6</sup> concerned men occupationally exposed to beryllium, some of whom developed acute beryllium disease. The populations for these studies come from two beryllium refining and smelting plants, and both show a 1.5 to 2-fold increase in lung cancer mortality. The statistically significant excess of lung cancer mortality was limited to men employed for less than 1 year, and only became apparent after a follow-up of 15 years or more. There was no increase in risk with increased duration of employment. None of the studies adequately consider

---

<sup>1</sup> IARC Monographs, 1: 80-86, 1972.

<sup>2</sup> Ferber, K.H., Hill, W.J. & Cobb, D.A. (1976) An assessment of the effect of improved working conditions on bladder tumor incidence in a benzidine manufacturing facility. *Am. Ind. Hyg. Assoc. J.*, 37: 61-68

<sup>3</sup> IARC Monographs, 1: 17-28, 1972.

<sup>4</sup> Infante, P.F., Wagoner, J.K. & Sprince, N.L. (1979) Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. *Environ. Res.* (in press).

<sup>5</sup> Mancuso, T.F. (1979) Occupational lung cancer among beryllium workers. *Environ. Res.* (in press)

<sup>6</sup> Wagoner, J.K., Bayliss, D.L. & Infante, P.F. (1979) Beryllium: An etiologic agent in the induction of lung cancer, non-neoplastic respiratory disease and heart disease among industrially exposed workers. *Environ. Res.* (in press).

the effects of smoking. The study that uses data from the Beryllium Case Registry<sup>1</sup> shows that six of the seven lung cancer deaths were in men whose exposure to beryllium was through refining and smelting, thus none of the studies can rule out the effects of factors other than beryllium in the working environment.

12. *N,N*-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE) (Group 1)

*N,N*-Bis(2-Chloroethyl)-2-naphthylamine (chlornaphazine) produces lung tumours in mice following intraperitoneal injection, and local sarcomas in rats after subcutaneous administration<sup>2</sup>.

The administration of chlornaphazine together with radioactive phosphorus (<sup>32</sup>P-sodium phosphate) caused bladder cancer in 10 of 61 patients treated for polycythemia vera. In 46 patients treated with <sup>32</sup>P-sodium phosphate alone, no cases of bladder cancer were found<sup>2</sup>.

13. BIS(CHROMETHYL)ETHER AND TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (Group 1)

Bis(chloromethyl)ether (BCME) produces tumours at the site of application in mice after administration by inhalation, skin application or subcutaneous injection, and in rats after inhalation and subcutaneous administration. Technical grade chloromethyl methyl ether (CMME) (which is almost always contaminated with BCME) produces local sarcomas in mice after subcutaneous administration, and is also an initiator of skin tumours<sup>3</sup>.

Two studies of workers exposed to BCME and technical grade CMME showed an increased risk of lung cancer, mainly oat-cell carcinoma<sup>3</sup>. Two subsequent studies have shown a positive association between atypical cells in bronchial excretions (abnormal pulmonary cytology) and exposure

---

<sup>1</sup> Infante, P.F., Wagoner, J.K. & Sprince, N.L. (1979) Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. Environ. Res. (in press).

<sup>2</sup> IARC Monographs, 4: 119-124, 1974.

<sup>3</sup> IARC Monographs, 4: 231-245, 1974.

to BCME<sup>1,2</sup> which was not related to cigarette smoking. Several studies have demonstrated a significant excess of lung cancer among BCME- or CMME-exposed workers<sup>2-5</sup> which was directly related to intensity and duration of exposure. Oat-cell carcinoma was the predominant histological type of lung cancer. The excess respiratory cancer mortality was most marked in workers under 55 years of age. The evaluation of CMME alone is complicated by the presence of 1% to 8% of BCME as a contaminant.

#### 14. CADMIUM AND CERTAIN CADMIUM COMPOUNDS (Group 2A)

Cadmium chloride, oxide, sulphate, and sulphide are carcinogenic in rats causing local sarcomas after subcutaneous injection. Cadmium powder and cadmium sulphide produce local sarcomas in rats following intramuscular administration. Cadmium chloride and cadmium sulphate produces testicular tumours in mice and rats following subcutaneous administration<sup>6</sup>.

Early studies suggested that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in humans. In addition, one of these studies suggested an increased risk of respiratory tract cancer<sup>6</sup>. A later study<sup>7</sup> showed a slight but not statistically significant increase in prostate cancer in battery plant workers (2 observed vs. 1.2 expected) and cadmium alloy workers (4 observed, vs. 2.69 expected).

---

<sup>1</sup> Frost, J.K., Gupta, P.K., Erozan, Y.F., Carter, D., Hollander, D.H. & Levin, M.L. (1973) Pulmonary cytology alterations in toxic environmental inhalation. *Hum. Pathol.*, 4: 521-536.

<sup>2</sup> Lemen, R.A., Johnson, W.M., Wagoner, J.K., Archer, V.E. & Saccomanno, G. (1976) Cytologic observations and cancer incidence following exposure to BCME. *Ann. N.Y. Acad. Sci.*, 271: 71-80.

<sup>3</sup> Sakabe, H. (1973) Lung cancer due to exposure to bis(chloromethyl) ether. *Ind. Health*, 11: 145-148.

<sup>4</sup> Albert, R.E., Pasternack, B.S., Shore, R.E., Lippmann, N.N. & Ferris, B. (1975) Mortality patterns among workers exposed to chloromethyl ethers - a preliminary report. *Environ. Health Perspect.*, 11: 209-214.

<sup>5</sup> Pasternack, B.S., Shore, R.E. & Albert, R.E. (1977) Occupational exposure to chloromethyl ethers. *J. Occup. Med.*, 19: 741-746.

<sup>6</sup> IARC Monographs, 11: 39-74, 1976.

<sup>7</sup> Kjellström, T., Friberg, L. & Rahnster, B. (1979) Mortality and cancer morbidity among cadmium-exposed workers: a preliminary report. *Environ. Health Perspect.*, 28: 199-204.

A case-control study<sup>1</sup> of renal cancer patients showed a 2.5-fold increased risk associated with occupational cadmium exposure. This relative risk doubled when cigarette smoking was included.

#### 15. CARBON TETRACHLORIDE (Group 2B)

Carbon tetrachloride is carcinogenic in mice and rats, producing liver tumours after administration by various routes. It also produced liver tumours in trout and hamsters following oral administration<sup>2</sup>.

Three case reports describe liver tumours associated with cirrhosis in humans exposed to carbon tetrachloride<sup>2</sup>.

#### 16. CHLORAMBUCIL (Group 2A)

Chlorambucil is carcinogenic in rats and mice following intraperitoneal injection, producing lymphomas in rats, and lymphosarcomas, ovarian tumours, and lung tumours in mice<sup>3</sup>.

Case reports have shown an association between chlorambucil treatment and development of leukaemia<sup>3</sup>. Women with ovarian cancer treated with a variety of alkylating agents, including chlorambucil, subsequently had an increased incidence of leukaemia<sup>4</sup>. Two cases of leukaemia and one case of renal clear-cell carcinoma have been reported in children treated for glomerulonephritis with chlorambucil<sup>5</sup>.

#### 17. CHLORAMPHENICOL (Group 3)

No data were available on the carcinogenicity of chloramphenicol in experimental animals.

---

<sup>1</sup> Kolonel, L.N. (1976) Association of cadmium with renal cancer. *Cancer*, 37: 1782-1789.

<sup>2</sup> IARC Monographs, 20: 1979 (in press).

<sup>3</sup> IARC Monographs, 9: 125-134, 1975.

<sup>4</sup> Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr, & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. *N. Engl. J. Med.*, 297: 177-181.

<sup>5</sup> Lenoir, G., Guesry, P., Kleinknecht, C., Gagnadoux, M.F. & Broyer, M. (1977) Complications extra-gonadiques du chlorambucil chez l'enfant (A propos de 300 observations de néphropathies glomérulaires traitées). *Arch. Fr. Pédiatr.*, 34, 798-807.



Case reports have described leukaemia in patients following chloramphenicol-induced aplastic anemia. A follow-up study described three cases of leukaemia in 126 patients who had bone marrow depression following treatment with chloramphenicol<sup>1</sup>.

#### 18. CHLORDANE AND HEPTACHLOR (Group 3)

These compounds are considered together, because they are structurally similar, and because they are often contaminated one with the other.

Chlordane and heptachlor (which contained about 20% chlordane) are carcinogenic in mice, producing liver tumours following oral administration. The data for rats are inconclusive<sup>2</sup>.

In one report, 5 out of 14 children with neuroblastoma had prenatal and/or postnatal exposure to chlordane. Exposure was not ascertained for the remaining 9 children. In an epidemiological study, three persons with acute leukaemia were found to have been exposed to chlordane (which contained 3% to 7% heptachlor)<sup>2</sup>.

#### 19. CHLOROPRENE (Group 3)

Tests for the carcinogenicity of chloroprene in animals were considered inadequate for evaluation<sup>3</sup>.

Epidemiological reports regarding cytogenic effects and reproductive disturbances in workers exposed to chloroprene and in their wives are consistent with experimental evidence that chloroprene is mutagenic. Several epidemiological studies regarding the carcinogenicity of chloroprene are inconclusive. There is one case report of angiosarcoma of the liver in a worker exposed to chloroprene<sup>3</sup>.

#### 20. CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS (Group 1)

Calcium chromate is carcinogenic in rats after administration by several routes, including intrabronchial implantation. Chromium chromate, strontium chromate, and zinc chromate produce local sarcomas

---

<sup>1</sup> IARC Monographs, 10: 85-98, 1976.

<sup>2</sup> IARC Monographs, 20: 1979 (in press).

<sup>3</sup> IARC Monographs, 19: 131-156, 1979.

in rats at the sites of application. The evidence for the carcinogenicity in mice and rats of barium chromate, lead chromate, chromic acetate, sodium dichromate and chromium carbonyl is inadequate<sup>1,2,3</sup>.

There is an increased incidence of lung cancer among workers in the chromate-producing industry<sup>1,4-7</sup> and possibly also among chromium platers<sup>8,9</sup> and chromium alloy workers<sup>10</sup>. There is also a suggestion of increased incidence of cancers at other sites<sup>8,10</sup>. The chromium compound(s) responsible has not been specified precisely.

- 
- <sup>1</sup> IARC Monographs, 2: 100-125, 1973.
  - <sup>2</sup> Ivankovic, S. & Preussmann, R. (1975) Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in sub-acute and long-term feeding experiments in rats. *Food Cosmet. Toxicol.*, 13: 347-351.
  - <sup>3</sup> Lane, B.P. & Mass, M.J. (1977) Carcinogenicity and cocarcinogenicity of chromium carbonyl in heterotopic tracheal grafts. *Cancer Res.*, 37: 1476-1479.
  - <sup>4</sup> Davies, J.M. (1978) Lung-cancer mortality of workers making chrome pigments. *Lancet*, i: 384.
  - <sup>5</sup> Langard, S. & Norseth, T. (1975) A cohort study of bronchial carcinomas in workers producing chromate pigments. *Br. J. Ind. Med.*, 32: 62-65.
  - <sup>6</sup> Ohsaki, Y., Abe, S., Kimura, K., Tsuneta, Y., Mikami, H. & Murao, M. (1978) Lung cancer in Japanese chromate workers. *Thorax*, 33: 372-374.
  - <sup>7</sup> Taylor, F.H. (1966) The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. *Am. J. Public Health*, 56: 218-229.
  - <sup>8</sup> Royle, H. (1975) Toxicity of chromic acid in the chromium plating industry (1). *Environ. Res.*, 10: 39-53.
  - <sup>9</sup> Waterhouse, J.A.H. (1975) Cancer among chromium platers. *Br. J. Cancer*, 32: 262.
  - <sup>10</sup> Pokrovskaya, L.V. & Shabynina, N.K. (1973) Carcinogenous hazards in the production of chromium ferroalloys. *Gig. Tr. Prof. Zabol.*, 10: 23-26.

## 21. CYCLOPHOSPHAMIDE (Group 2A)

Cyclophosphamide is carcinogenic in mice and rats following intraperitoneal injection, in rats following intravenous injection and in mice following subcutaneous injection. Dosages used were comparable to those used in clinical practice. It produced mainly lung and lymphoreticular tumours, but tumours of the liver and reproductive organs, sarcomas and squamous-cell carcinomas of the skin<sup>1</sup> and bladder tumours<sup>2</sup> were also observed.

There are a number of case reports of bladder cancer and acute myeloid leukaemia in persons treated with cyclophosphamide for a variety of medical conditions<sup>1</sup>. A prospective epidemiological study of women with ovarian cancer showed an increase of acute non-lymphocytic leukaemia following treatment with alkylating agents, including cyclophosphamide<sup>3</sup>.

## 22. DICHLORODIPHENYLTRICHLOROETHANE (DDT) (Group 3)

Dichlorodiphenyltrichloroethane (DDT) is carcinogenic in mice causing liver tumours following oral administration<sup>4</sup>. Non-metastasizing liver tumours occur in rats fed DDT<sup>5,6</sup>

The epidemiological studies available were considered to be inadequate to allow an evaluation of the carcinogenicity of DDT<sup>4</sup>.

---

<sup>1</sup> IARC Monographs, 9: 135-156, 1975.

<sup>2</sup> Schmähl, D. & Habs, M. (1979) Carcinogenic action of low-dose cyclophosphamide given orally to sprague-dawley rats in a lifetime experiment. *Int. J. Cancer*, 23: 706-712

<sup>3</sup> Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr, & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. *N. Engl. J. Med.*, 297: 177-181.

<sup>4</sup> IARC Monographs, 5: 83-124, 1974.

<sup>5</sup> Rossi, L., Ravera, M., Repetti, G. & Santi, L. (1977) Long-term administration of DDT or phenobarbital in Wistar rats. *Int. J. Cancer*, 19: 179-185.

<sup>6</sup> Cabral, J.R.P., Hall, R.K. & Shubik, P. (1978) Effects of long-term DDT intake in rats. Abstract presented at 20<sup>th</sup> Congress of the European Society of Toxicology, West Berlin, June 25-28, 1978.

## 23. DIELDRIN (Group 3)

Dieldrin is carcinogenic in mice, causing a dose-related increase in liver tumours following oral administration. Feeding studies in rats have shown no carcinogenic effect<sup>1,2</sup>.

A study of workers exposed to dieldrin involved too few subjects and insufficient follow-up time to allow an evaluation of carcinogenicity<sup>1</sup>.

## 24. DIETHYLSTILBOESTROL (Group 1)

Diethylstilboestrol is carcinogenic in mice, rats, hamsters, frogs<sup>3</sup>, and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues<sup>4</sup>.

Diethylstilboestrol causes clear-cell carcinoma of the vagina in females exposed *in utero*<sup>4,5</sup>. The evidence for an association with other human cancers is either limited (endometrium)<sup>6</sup> or inadequate (breast<sup>6</sup>, ovary<sup>7</sup>).

---

<sup>1</sup> IARC Monographs, 5: 125-156, 1974.

<sup>2</sup> Stevenson, D.E., Thorpe, E., Hunt, P.F. & Walker, A.I.T. (1976)  
The toxic effects of dieldrin in rats: a reevaluation of data  
obtained in a two-year feeding study. *Toxicol. Appl. Pharmacol.*,  
36: 247-254.

<sup>3</sup> Khudoley, V.V. (1976) Carcinogenic action of diethylstilbestrol on  
frogs. *Exp. Biol. Med.*, 81: 898-900.

<sup>4</sup> IARC Monographs, 6: 55-76, 1974. (IARC Monographs, 21: in preparation)

<sup>5</sup> Herbst, A.L., Cole, P., Colton, T., Robboy, S.J. & Scully, R.E.  
(1977) Age-incidence and risk of diethylstilbestrol-related  
clear cell adenocarcinoma of the vagina and cervix. *Am. J.*  
*Obstet. Gynecol.*, 128: 43-50.

<sup>6</sup> Bibbo, M., Haenszel, W.M., Wied, G.L., Hubby, M. & Herbst, A.L.  
(1978) A twenty-five-year follow-up study of women exposed  
to diethylstilbestrol during pregnancy. *N. Engl. J. Med.*,  
298: 763-767.

<sup>7</sup> Hoover, R., Gray, L.A. & Fraumeni, J.F. Jr. (1977) Stilboestrol  
(diethylstilboestrol) and the risk of ovarian cancer. *Lancet*,  
ii: 533-534.

## 25. DIMETHYLCARBAMOYL CHLORIDE (Group 2B)

Dimethylcarbamoyl chloride is carcinogenic in mice, producing local carcinomas after application to the skin and local sarcomas after subcutaneous or intraperitoneal injection<sup>1</sup>.

A study of humans exposed to dimethylcarbamoyl chloride was considered inadequate due to the small number of people observed<sup>1</sup>.

## 26. DIMETHYL SULPHATE (Group 2B)

Dimethyl sulphate is carcinogenic in rats after inhalation or subcutaneous injection, producing mainly local tumours, and after prenatal exposure, producing tumours of the nervous system<sup>2</sup>.

Four bronchial carcinomas have been reported in men occupationally exposed to dimethyl sulphate<sup>2</sup>. In an epidemiological study six cancer deaths were found *versus* 2.4 expected; three of these were cancers of the respiratory tract (1.02 expected)<sup>3</sup>. Neither the respiratory tract cancers nor the cancer rate at all sites are statistically significantly increased.

## 27. EPICHLOROHYDRIN (Group 3)

Epichlorohydrin produces local sarcomas in mice following subcutaneous injection, and was active as an initiator in a two-stage carcinogenesis study in mice<sup>4</sup>.

Among men exposed to epichlorohydrin for 15 years or more at 2 plants there was an increased number of deaths due to respiratory cancer (8 observed, 4.7 expected) and leukaemia (2 observed, 0.4 expected)<sup>5</sup>. This excess was not statistically significant and furthermore cannot be attributed confidently to epichlorohydrin exposure alone, since these men were exposed to other chemicals, and since smoking habits were not considered in the analysis.

---

<sup>1</sup> IARC Monographs, 12: 77-84, 1976.

<sup>2</sup> IARC Monographs, 4: 271-276, 1974.

<sup>3</sup> Pell, S. (1979 - submitted for publication) Mortality of workers exposed to dimethyl sulphate, 1932-1974. Am. Ind. Hyg. Assoc. J.

<sup>4</sup> IARC Monographs, 11: 131-139, 1976.

<sup>5</sup> Enterline, P.E. & Henderson, V.L. (1979) Updated mortality in workers exposed to epichlorohydrin. J. Occup. Med. (in press)

## 28. ETHYLENE OXIDE (Group 2B)

Solutions of ethylene oxide have been tested inadequately in mice by skin application and in rats by subcutaneous injection. No experiments involving inhalation were available<sup>1</sup>.

Two studies of human populations exposed occupationally to ethylene oxide<sup>2,3</sup> have shown increased rates of leukaemia. One of these studies also showed increased rates of gastric cancer. These increases cannot confidently be attributed to ethylene oxide alone however, since the workers were also exposed to other chemicals.

## 29. HAEMATITE (Group 3) AND

## 30. UNDERGROUND HAEMATITE MINING (Group 1)

No carcinogenic effects were observed in mice, hamsters, or guinea-pigs given ferric oxide intratracheally<sup>4</sup>.

Underground haematite miners have a high incidence of lung cancer, whereas surface haematite miners do not. It is not known whether this excess risk may be due to haematite; to radon (a known lung carcinogen); to inhalation of ferric oxide or silica; or to a combination of these or other factors. Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer, while other studies have not<sup>4,5</sup>. The influence of factors in the workplace other than ferric oxide cannot be eliminated.

## 31. HEXACHLOROCYCLOHEXANE (TECHNICAL HCH AND LINDANE) (Group 3)

Technical HCH,  $\alpha$ - and  $\beta$ -HCH and lindane ( $\gamma$ -HCH) are carcinogenic in mice when administered orally, producing liver tumours. Studies in rats were considered inadequate<sup>6</sup>.

Approximately 30 cases of aplastic anaemia, and 3 cases of acute myeloid leukaemia have been reported following exposure to HCH or lindane. A study of 285 workers exposed to many pesticides (including HCH and lindane) showed an apparent excess of lung tumours and one case of leukaemia; however, this cannot be attributed to exposure to HCH or lindane alone<sup>6</sup>.

---

<sup>1</sup> IARC Monographs, 11: 157-168, 1976.

<sup>2</sup> Hogstedt, C., Rohlén, O., Berndtsson, B.S., Axelson, O. & Ehrenberg, L. (1978) Kohortstudie av dödsorsaker hos anställda i etylenoxidframställning. *Läkartidningen*, 75: 3285-3287.

<sup>3</sup> Hogstedt, C., Malaqvist, N. & Wadman, B. (1979) Leukemia in workers exposed to ethylene oxide. *JAMA*, 241: 1132-1133.

<sup>4</sup> IARC Monographs, 1: 29-39, 1972.

<sup>5</sup> Axelson, O. & Sjöberg, A. (1979) Cancer incidence and exposure to iron oxide dust. *J. Occup. Med.*, 21: 419-422.

<sup>6</sup> IARC Monographs, 20: 1979 (in press).

## 32. IRON DEXTRAN (Group 2B)

Iron dextran is carcinogenic in mice and rats after subcutaneous or intramuscular injection, producing local tumours<sup>1</sup>.

There have been case reports of sarcomas associated with injections of iron dextran<sup>1,2</sup>. The tumours appeared at the probable site of the injections, and the similarity of the local effect in humans and animals was noted.

## 33. ISONIAZID (Group 3)

Isoniazid produces lung tumours in mice after oral, intraperitoneal, or subcutaneous administration. Studies in rats and hamsters were considered inadequate<sup>3</sup>.

Several early studies failed to show a significant excess of cancer among patients treated with isoniazid<sup>3</sup>. A study of tuberculosis patients<sup>4</sup>, most of whom were followed for more than 19 years, showed a slight excess of respiratory cancers in patients treated with isoniazid, (relative risk = 1.4, 95% confidence limits 1.03 to 1.96 calculated by the Secretariat) and a deficit in patients not treated with isoniazid (relative risk = 0.3, 95% confidence interval 0.06 to 0.91 calculated by the Secretariat). Although the numbers are small, the effect was similar in both groups examined, and was not seen for cancers at sites other than respiratory. The excess was mainly for deaths within 4 years of the start of isoniazid therapy. No dose response effect was seen either for total consumption or maximum daily dose. The striking differences in mortality between patients treated earlier in the study and those treated later, and the uncertain relationship of tuberculosis to lung cancer in the absence of isoniazid therapy make these data difficult to evaluate. In a case-control study<sup>5</sup> of patients with bladder cancer it was found that an excess of female cases but a deficit of male cases had previously taken isoniazid compared to controls without bladder cancer; however, the numbers were small and the results were not statistically significant.

---

<sup>1</sup> IARC Monographs, 2: 161-178, 1973.

<sup>2</sup> Greenberg, G. (1976) Sarcoma after intramuscular iron injection. Br. Med. J., ii: 1508-1509.

<sup>3</sup> IARC Monographs, 4: 159-172, 1974.

<sup>4</sup> Stott, H., Peto, J., Stephens, R. & Fox, W. (1976) An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. Tubercle, 57: 1-15.

<sup>5</sup> Miller, C.T., Neutel, C.I., Nair, R., Marrett, L.D., Last, J.M. & Collins, W.E. (1978) Relative importance of risk factors in bladder carcinogenesis. J. Chronic. Dis., 31: 51-56.

## 34. ISOPROPYL OILS (Group 3) AND

## 35. THE MANUFACTURE OF ISOPROPYL ALCOHOL (STRONG ACID PROCESS) (Group 1)

Isopropyl oils, formed during the manufacture of isopropyl alcohol by both the strong-acid and the weak-acid processes, were tested inadequately in mice by inhalation, skin application, and subcutaneous administration. Isopropyl oils (strong-acid process) were also tested inadequately in dogs by inhalation and by instillation into the sinuses<sup>1</sup>.

An increased incidence of cancer of the paranasal sinuses has been found in workers in factories manufacturing isopropyl alcohol by the strong-acid process in which isopropyl oils were formed as by-products<sup>1</sup>.

## 36. LEAD AND CERTAIN LEAD COMPOUNDS (Group 3)

Basic lead acetate is carcinogenic in rats and mice after oral administration, producing renal tumours. Lead acetate, lead subacetate, and lead phosphate are carcinogenic in rats, producing renal tumours after oral, intraperitoneal or subcutaneous administration<sup>2</sup>. Other lead salts have been inadequately tested<sup>3,4</sup>. No studies of organic lead compounds in animals were available.

An early epidemiological study provided no evidence that exposure to lead or lead compounds caused cancer in humans<sup>2</sup>. One prospective study of mortality in workers in lead smelters and battery plants showed respectively a 30% and 11% increased mortality from all malignant neoplasms<sup>5</sup>. The findings were statistically significant only in the smelter workers. An excess of tumours was seen in the respiratory, urinary, and digestive system, although none of these were significantly increased when considered alone. A study of tetraethyllead workers is inadequate because only workers who remained employed during the study period were included<sup>6</sup>.

---

<sup>1</sup> IARC Monographs, 15: 223-243, 1977.

<sup>2</sup> IARC Monographs, 1: 40-50, 1972.

<sup>3</sup> Coogan, P., Stein, L., Hsu, G. & Hass, G. (1972) The tumorigenic action of lead in rats. *Lab. Invest.*, 26: 473.

<sup>4</sup> Ito, N. (1973) Experimental studies on tumors of the urinary system of rats induced by chemical carcinogens. *Acta Pathol. Jpn*, 23: 87-109.

<sup>5</sup> Cooper, W.C. & Gaffy, W.R. (1975) Mortality of lead workers. *J. Occup. Med.*, 17: 100-107.

<sup>6</sup> Robinson, T.R. (1976) The health of long service tetraethyl lead workers. *J. Occup. Med.*, 18: 31-40.



(The working group noted that while human exposure was mainly to metallic lead, the animal carcinogenicity data concerned soluble lead salts. Thus even with sufficient evidence in animals, lead and lead compounds were classified in group 3).

### 37. MELPHALAN (Group 1)

Melphalan is carcinogenic in mice and rats following intraperitoneal injection, producing lymphosarcomas, a dose-related increase in lung tumours in mice, and peritoneal sarcomas in rats<sup>1</sup>.

Case reports of second primary malignancies (mainly acute leukaemia) in patients treated with melphalan have been published<sup>1-5</sup>. Epidemiological studies showed substantially increased rates of leukaemia in patients treated with melphalan for multiple myeloma<sup>6</sup> and ovarian cancer<sup>7,8</sup>. Some of these patients were also treated with other alkylating agents and ionizing radiation, however sufficient numbers of patients were treated with melphalan alone to implicate it as the causal factor. Additionally the incidence of acute leukaemia in patients with multiple myeloma has increased since the introduction of melphalan therapy<sup>9</sup>.

- 
- <sup>1</sup> IARC Monographs, 9: 167-180, 1975.
  - <sup>2</sup> Bell, R., Sullivan, J.R., Fone, D.J. & Hurley, T.H. (1976) Carcinoma of the breast. Occurrence after treatment with melphalan for multiple myeloma. *J. Assoc. Off. Anal. Chem.*, 236: 1609-1610.
  - <sup>3</sup> Burton, I.E., Abbot, C.R., Roberts, B.E. & Antonis, A.H. (1976) Acute leukaemia after four years of melphalan treatment for melanoma. *Br. Med. J.*, i: 20.
  - <sup>4</sup> Buskard, N.A., Boyes, D.A. & Grossman, L. (1977) Plasma cell leukemia following treatment with radiotherapy and melphalan. *Can. Med. Assoc. J.*, 117: 788-789.
  - <sup>5</sup> De Bock, R.F.K. & Peetermans, M.E. (1977) Leukaemia after prolonged use of melphalan for non-malignant disease. *Lancet*, i: 1208-1209.
  - <sup>6</sup> Law, I.P. & Blom, J. (1977) Second malignancies in patients with multiple myeloma. *Oncology*, 34: 20-24.
  - <sup>7</sup> Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. *N. Engl. J. Med.*, 297: 177-181.
  - <sup>8</sup> Einhorn, N. (1978) Acute leukemia after chemotherapy (melphalan). *Cancer*, 41: 444-447.
  - <sup>9</sup> Adamson, R.H. & Sieber, S.M. (1977) Antineoplastic agents as potential carcinogens. In: Hiatt, H., Watson, J. & Winsten, J. eds, *Origins of Human Cancer*, Cold Spring Harbour Laboratory, pp. 429-444.

## 38. MUSTARD GAS (Group 1)

Mustard gas is carcinogenic in mice, the only species tested, after inhalation or intravenous injection producing lung tumours, and after subcutaneous injection producing local sarcomas<sup>1</sup>.

Several studies have shown an increased mortality from respiratory tract cancer among individuals exposed to mustard gas. This mortality was greater in those with chronic occupational exposure than in those with sporadic exposure<sup>1</sup>.

## 39. 2-NAPHTHYLAMINE (Group 1)

2-Naphthylamine is carcinogenic, producing urinary bladder carcinomas in hamsters, dogs, and non-human primates, and hepatomas in mice, after oral administration<sup>2</sup>.

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is causally associated with bladder cancer<sup>2</sup>.

## 40. NICKEL, CERTAIN NICKEL COMPOUNDS (Group 2A) AND

## 41. NICKEL REFINING (Group 1)

Nickel subsulphide is carcinogenic in rats by inhalation, producing lung cancer. Nickel compounds (nickel powder, subsulphide, oxide carbonate, and nickelocene) produced local sarcomas in mice, rats and hamsters when given intramuscularly. Inhalation of nickel carbonyl produced a low incidence of lung tumours in rats<sup>3</sup>.

Epidemiological studies have demonstrated increased incidences of cancer of the nasal cavity, lung, and possibly larynx in workers in nickel refineries. It is not possible, however, to state with certainty which specific nickel compound(s) is carcinogenic for humans<sup>3</sup>.

---

<sup>1</sup> IARC Monographs, 9: 181-192, 1975.

<sup>2</sup> IARC Monographs, 4: 97-111, 1974.

<sup>3</sup> IARC Monographs, 11: 75-112, 1976.

## 42. OXYMETHOLONE (Group 2B)

No data from experimental animal studies were available to the Working Group<sup>1</sup>.

Ten cases of liver-cell tumours have been reported in patients with blood disorders treated for long periods with oxymetholone alone or in combination with other androgenic drugs; however, a causal relationship cannot be established. The increased risk of liver-cell tumours could be related to hepatic damage known to be caused by oxymetholone. Alternatively, patients with congenital anaemias may be at higher risk of developing these tumours, and this risk may become manifest during the extended survival resulting from oxymetholone treatment<sup>1</sup>.

## 43. PHENACETIN (Group 2B)

Rats fed a diet containing phenacetin had an excess of nasal and urinary tract tumours<sup>2</sup>. *N*-hydroxyphenacetin (a possible metabolite of phenacetin) produced liver carcinomas in rats following oral administration<sup>3</sup>.

Several studies indicate that the chronic abuse of analgesic mixtures containing phenacetin is associated with papillary necrosis of the kidney, and suggest a relationship between papillary necrosis and the subsequent development of transitional-cell carcinoma of the renal pelvis<sup>3</sup>. These compounds contain phenacetin with other anti-inflammatory drugs (often salicylates or antipyrine (phenazone)) and caffeine.

## 44. PHENOBARBITONE (Group 3)

Phenobarbitone sodium is carcinogenic, producing benign and malignant liver-cell tumours in mice and benign liver-cell tumours in rats after oral administration<sup>4</sup>.

---

<sup>1</sup> IARC Monographs, 13: 131-139, 1977.

<sup>2</sup> Isaka, H., Yoshii, H., Otsuji, A. et al. (1979) Tumours of Sprague-Dawley rats induced by long-term feeding of phenacetin. *Gann*, 70: 29-36.

<sup>3</sup> IARC Monographs, 13: 141-155, 1977.

<sup>4</sup> IARC Monographs, 13: 157-181, 1977.

A possible relationship between anticonvulsant therapy in which phenobarbitone was included and the occurrence of cancer in humans has been investigated in one epidemiological study and reported in several case studies. In most instances, phenobarbitone was given in conjunction with other drugs, in particular phenytoin<sup>1</sup>. A further follow-up<sup>2</sup> of the patients from this study (who were hospitalized for long periods for the treatment of epilepsy) showed an excess of brain tumours, even more than 10 years after the diagnosis of epilepsy (12 observed versus 4.3 expected), and an increase in liver tumours (11 observed versus 2.8 expected). However, eight of the 11 liver tumour patients also received Thorotrast, a known liver carcinogen. Furthermore, the appearance of brain tumours in these patients is difficult to interpret, because they may be due to the underlying medical condition, rather than to the drugs *per se*. No excess of malignancies of any other sites were seen. In another epidemiological study<sup>3</sup> significantly more mothers of children with brain tumours used "barbiturates" (unspecified) when compared with the mothers of children with other cancers, but not when compared with the mothers of normal children. The reason these drugs were given was not specifically stated (see also Phenytoin).

45. *N*-PHENYL-2-NAPHTHYLAMINE (Group 3)

*N*-Phenyl-2-naphthylamine was tested inadequately in mice by oral administration or by single subcutaneous injection. In a biotransformation study, 0.02% of a measured dose of *N*-phenyl-2-naphthylamine was converted metabolically to 2-naphthylamine in dogs<sup>4</sup>.

No excess of bladder tumours was found in men in a rubber processing factory with known exposure to *N*-phenyl-2-naphthylamine (which contained small amounts of 2-naphthylamine). However, a different study of rubber workers (who were not exposed to 2-naphthylamine) did show an increase of bladder tumours. In the latter study, exposure was to several compounds, which probably included *N*-phenyl-2-naphthylamine. These findings do not permit an assessment of the carcinogenicity of *N*-phenyl-2-naphthylamine. There is limited evidence from one study of 19 human volunteers that 0.03% of a single 10 mg dose of *N*-phenyl-2-naphthylamine was converted to 2-naphthylamine, a known bladder carcinogen<sup>4</sup>.

---

<sup>1</sup> IARC Monographs, 13: 157-181, 1977.

<sup>2</sup> Clemmesen, J. & Hjalgrim-Jensen, S. (1978) Is phenobarbital carcinogenic? A follow-up of 8078 epileptics. *Exotoxicol. Environ. Safety*, 1, 457-470.

<sup>3</sup> Gold, E., Gordis, L., Tonascia, J. & Szkio, M. (1978) Increased risk of brain tumors in children exposed to barbiturates. *J. Natl Cancer Inst.*, 61: 1031-1034.

<sup>4</sup> IARC Monographs, 16: 325-341, 1978.

## 46. PHENYTOIN (Group 3)

Phenytoin is carcinogenic in mice after oral administration or by intraperitoneal injection, producing lymphomas and leukaemias<sup>1</sup>.

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin<sup>1</sup>; however, no excess of lymphomas was reported in a follow-up study of epilepsy patients, many of whom received phenytoin along with other anti-epileptic drugs<sup>2</sup>. Three recent papers<sup>3,4,5</sup> report one case of malignant mesenchymoma and two cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study<sup>6</sup> looked at the frequency of use of phenytoin and of phenobarbitone in mothers of children with childhood cancers compared with mothers of normal children. While more mothers of cancer cases reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers who took either phenytoin or phenobarbitone. An excess of lymphomas (6 observed, 4 expected) was seen in children of epileptic mothers, but the occurrence of brain tumours was not reported (see also Phenobarbitone).

## 47. POLYCHLORINATED BIPHENYLS (Group 2B)

Certain polychlorinated biphenyls are carcinogenic in mice and rats after oral administration, producing liver tumours<sup>7</sup>

A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Arochlor 1254, a mixture of polychlorinated biphenyls<sup>7</sup>.

---

<sup>1</sup> IARC Monographs, 13: 201-225, 1977.

<sup>2</sup> Clemmesen, J. & Hjalmsgrim-Jensen, S. (1978) Is phenobarbital carcinogenic: a follow-up of 8078 epileptics. *Exotoxicol. Environ. Safety*, 1: 457-470,

<sup>3</sup> Pendergrass, T.W. & Henson, J.W. (1976) Fetal hydantoin syndrome and neuroblastoma. *Lancet*, ii, 150.

<sup>4</sup> Sherman, S. & Roizen, N. (1976) Fetal hydantoin syndrome and neuroblastoma. *Lancet*, ii, 517.

<sup>5</sup> Blattner, W.A., Henson, D.E., Young, R.C. & Fraumeni, J.F. Jr, (1977) Malignant mesenchymoma and birth defects. Prenatal exposure to phenytoin. *JAMA*, 238: 334-335.

<sup>6</sup> Sanders, B.M. & Draper, G.J. (1979) Childhood cancer and drugs in pregnancy. *Br. Med. J.*, i: 717-718.

<sup>7</sup> IARC Monographs, 18: 43-103, 1978.

## 48. RESERPINE (Group 3)

Reserpine has been tested inadequately in mice and rats by oral administration<sup>1</sup>.

Thirteen case-control studies were available to the working group<sup>1-8</sup>. Most report a relative risk of between 1 and 2 for breast cancer associated with the use of reserpine. Patients who had taken reserpine for more than 5 years had slightly higher relative risks. In 11 of the 13 studies the relative risks were not statistically significant, although pooling of the studies gave a summary relative risk of 1.2 with 95% confidence intervals 1.1 to 1.4. The possibility of confounding due to several medical care variables could not be excluded, hence none of the studies, either singly or pooled, provide conclusive evidence of a causal association.

---

<sup>1</sup> IARC Monographs, 10: 217-229, 1976.

<sup>2</sup> Lilienfeld, A.M., Chang, L., Thomas, D.B. & Levin, M.L. (1975) Rauwolfia derivatives and breast cancer. *Johns Hopkins Med. J.*, 139: 41-50.

<sup>3</sup> Armstrong, B., Skegg, D., White, G. & Doll, R. (1976) Rauwolfia derivatives and breast cancer in hypertensive women. *Lancet*, ii: 8-12.

<sup>4</sup> Aromaa, A., Hakama, M., Hakulinen, T., Saxen, E., Teppo, L. & Idänpään-Heikkilä, J. (1976) Breast cancer and use of rauwolfia and other antihypertensive agents in hypertensive patients: a nationwide case-control study in Finland. *Int. J. Cancer*, 18: 727-738.

<sup>5</sup> Christopher, L.J., Crooks, J., Davidson, J.F., Erskine, Z.G., Gallon, S.C., Moir, D.C. & Weir, R.D. (1977) A multi-centre study of rauwolfia derivatives and breast cancer. *Eur. J. Clin. Pharmacol.*, 11: 409-417.

<sup>6</sup> Kodlin, D. & McCarthy, N. (1978) Reserpine and breast cancer. *Cancer*, 41: 761-768.

<sup>7</sup> Williams, R., Feinleib, M., Connor, R. & Stegens, N. (1978) Case-control study of antihypertensive and diuretic use by women with malignant and benign breast lesions detected in a mammography screening program. *J. Natl Cancer Inst.*, 61: 327-335.

<sup>8</sup> Kewitz, H., Jesdinsky, H., Schröter, P. & Lindtner, E. (1977) Reserpine and breast cancer in women in Germany. *Eur. J. Clin. Pharmacol.*, 11: 79-83.

## 49. SOOTS, TARS AND MINERAL OILS (Group 1)

Soots, coal-tars, creosote oils, shale oils and cutting oils are carcinogenic in experimental animals after skin painting or subcutaneous injection<sup>1</sup>.

Occupational exposure to coal-soot, coal-tar and pitch, coal-tar fumes and some impure mineral oils causes cancer of several sites, including skin, lung, bladder, and gastrointestinal tract<sup>1</sup>. Recent epidemiological data have supported these conclusions<sup>2-7</sup>. This effect may be due to the presence of polycyclic aromatic hydrocarbons in these materials.

## 50. STYRENE (Group 3)

Styrene produces lung tumours in mice following oral administration<sup>8,9</sup>.

Three deaths from leukaemia and 2 from lymphoma have been reported in workers exposed to styrene, benzene and butadiene; however, these deaths cannot be attributed to styrene exposure alone<sup>8</sup>.

---

<sup>1</sup> IARC Monographs, 3: 22-42, 1973.

<sup>2</sup> Decoufle, P. (1978) Further analysis of cancer mortality among workers exposed to cutting oil mist. *J. Natl Cancer Inst.*, 61: 1025-1030.

<sup>3</sup> Hammond, E.C., Selikoff, I.J., Lawther, P.L. & Seidman, H. (1976) Inhalation of benzpyrene and cancer in man. *Ann. N.Y. Acad. Sci.*, 271: 116-124.

<sup>4</sup> McMichael, A.J., Spirtas, R., Gamble, J.F. & Tousey, P.M. (1976) Mortality among rubber workers: Relationship to specific jobs. *J. Occup. Med.*, 18: 178-185.

<sup>5</sup> Redmond, C.K., Strobino, B.R. & Cypress, R.H. (1976) Cancer experience among coke byproduct workers. *Ann. N.Y. Acad. Sci.*, 271: 102-115.

<sup>6</sup> Andjelkovich, D., Taulbee, J., Symons, M. & Williams, T. (1977) Mortality of rubber workers with reference to work experience. *J. Occup. Med.*, 19: 397-405.

<sup>7</sup> Wigle, D.T. (1977) Bladder cancer: Possible new high-risk occupation. *Lancet*, ii: 83-84.

<sup>8</sup> IARC Monographs, 19: 231-274, 1979.

<sup>9</sup> National Cancer Institute (1979) Bioassay of styrene for possible carcinogenicity. Tech. Rep. Series No. 185 DHEW Pub. No. (NIH) 79-1741, Washington, D.C.

## 51. TRICHLOROETHYLENE (Group 3)

Trichloroethylene is carcinogenic in mice after oral administration, producing hepatocellular carcinomas and lung tumours<sup>1</sup>.

An epidemiological study of mortality in men occupationally exposed to trichloroethylene showed no excess of cancer deaths<sup>1</sup>.

52. TRIS(AZIRIDINYL)-*para*-BENZOQUINONE (TRIAZIQUONE) (Group 3)

Tris(aziridinyl)-*para*-benzoquinone (triaziquone) is carcinogenic in rats after intravenous or combined intravenous and intraperitoneal injection, producing a variety of malignant tumours<sup>2</sup>.

The four available case reports were inadequate to evaluate the carcinogenicity of triaziquone<sup>2</sup>.

## 53. TRIS(1-AZIRIDINYL)PHOSPHINE SULPHIDE (THIOTEPA) (Group 2A)

Tris(1-aziridinyl)phosphine sulphide (thiotepa) is carcinogenic in mice and rats after administration by various routes, producing a variety of malignant tumours<sup>3,4</sup>.

There are several reports and epidemiological studies suggesting the development of acute non-lymphocytic leukaemia in patients treated with thiotepa for ovarian and other malignant tumours<sup>3,5</sup>.

---

<sup>1</sup> IARC Monographs, 20: 1979 (in press).

<sup>2</sup> IARC Monographs, 9: 67-73, 1975.

<sup>3</sup> IARC Monographs, 9: 85-94, 1975.

<sup>4</sup> National Cancer Institute, Bioassay of Thiotepa for possible carcinogenicity. Tech. Rep. Series No. 58, DHEW Pub. No. (NIH) 78-1308, Washington, D.C., 168 pp.

<sup>5</sup> Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., 297: 177-181.



## 54. VINYL CHLORIDE (Group 1)

Vinyl chloride is carcinogenic in mice, rats and hamsters after administration orally or by inhalation, producing tumours at several sites, including angiosarcomas of the liver<sup>1</sup>.

Vinyl chloride causes angiosarcomas of the liver, and tumours of the brain, lung, and haematolymphopoietic system in humans<sup>1</sup>. Reports of increases in digestive system, urinary system and breast tumours (in women) are inadequate to evaluate carcinogenicity for these sites<sup>1</sup>.