TOXICITY OF INDUSTRIAL METALS

SECOND EDITION

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reverberatory furnace, with small amounts of iron pyrites or galena. When cooled by passage through a series of brick chambers, the oxide condenses as a crude product to be purified by re-sublimation (Buchanan, 1961).

Arsenic can also be prepared from mispickel by heating in earthenware retorts and distilling off the arsenic condensed on sheet iron in the neck of the retort. It can also be obtained, free from oxide, by reducing pure As_2O_3 with zirconium.

PROPERTIES

In its stable form arsenic is a steel-gray, brittle, crystalline metalloid. It exhibits allotropy, the two other forms usually distinguished being yellow and black respectively. It forms three oxides—the trioxide, As_2O_3 (the most abundant commercial source of arsenical compounds); the pentoxide, As_2O_5 (the primary material for many arsenical insecticides); and the tetroxide, As_2O_4. Atomic number, 18; atomic weight, 74·91; specific gravity, 5·73 (yellow allotrope 3·7, black allotrope 4·7; threshold limit value 0·5 mg. per c.m.).

PROPERTIES OF ARSENIC TRIOXIDE (THE PRINCIPAL COMPOUND)

The crude arsenic trioxide dust obtained by sublimation during smelting of arsenic-containing ores consists of approximately 97 per cent of As_2O_3, its principal impurity being antimony trioxide. Pinto and McGill (1953) stated that the particle size of over 23 per cent of the dust is over 5·5μ. It is only slightly soluble in water but soluble in alkaline and acid solutions. It was stated by Schwartze (1922) that the toxicity of arsenic trioxide was inversely proportional to the particle size, the oral $L.D._{50}$ for the rat varying between 75 and 500 mg. of arsenic per kg. according to the size.

Other *inorganic compounds* of arsenic include arsenic chloride, ("butter of arsenic"), a colourless oily liquid used chiefly in the manufacture of pharmaceuticals; arsenites, arsenates and sulphur compounds. The arsenite salts in which the acid corresponds to arsenious and arsenic acids, while of the alkali salts, sodium meta-arsenate, which is readily soluble in water, is the most widely used. Of the arsenates, those of lead, calcium and magnesium are mainly used as spray insecticides, and in recent years magnesium arsenate has been found of value in the manufacture of fluorescent lamps.

The sulphur compounds, As_2S_3 (orpiment) and realgar (As_2O_2) have been largely supplanted as pigments by lead chromes, and as a depilatory realgar has been generally replaced by sodium sulphide.

Arsenical pigments—copper arsenite (Scheele's Green) and copper aceto arsenite (Schweinfurte Green) were formerly widely used as pigments in wall-paper, calico printing and as wood preservatives, but their use for these purposes is now much diminished, partly on account of the liberation of the toxic gas dimethyl arsine by the action of moulds.

Organic compounds of arsenic.—The arsphenamines—Salvarsan and Neosalvarsan—derived from diarsenobenzene, are best known for their therapeutic effects in protozoal diseases, which were first demonstrated following the discovery that atoxyl (sodium arsenilate) had this property, but they have now been largely supplanted by antibiotics.

ESTIMATION OF ARSENIC

In estimating trace amounts of arsenic in biological or industrial material, it must be rendered soluble. Thereafter, there are several very well-known chemical tests—Reinsch, Marsh and Gutzeit—described in detail in standard works on analytical chemistry, and more concisely by Buchanan (1961).

Estimation by radioactivation was first described by Smales and Pate (1952) and adapted by Lenihan and Smith (1958). The sample to be irradiated is placed in an atomic pile, then converted into arsine, which is absorbed in a solution of mercury chloride and examined by a Geiger counter. Estimation by neutron activation analysis is described by Krishnan, S. S. *et al.* (1966).

INDUSTRIAL USES

Arsenic is used industrially for the following purposes.

(1) In the manufacture of insecticides, weed killers and fungicides (usually in the form of potassium arsenite), and as a wood preservative.

(2) In glass manufacture as a bronzing or decolorizing addition, and in the production of opal glass and enamels, particularly in the majolica industry in Italy (Dechigi, 1936).

(3) As an addition to alloys in amounts of 0·3–0·5 per cent to increase hardening and heat resistance.

(4) In the manufacture of arsenical organic compounds for therapeutic use.

MAXIMUM ALLOWABLE CONCENTRATION

The MAC recommended by the American Conference of Governmental Industrial Hygienists in 1962 and not since revised is as follows:

Arsenic (dust) 0·5 mg. per c.m.
Arsine 0·05 p.p.m. (0·2 mg. per c.m.).

METABOLISM

Although arsenic is not an essential element of human metabolism, it is, owing to its wide distribution in nature, constantly taken into the human body in very small quantities, and is therefore regarded by most authorities as a normal constituent of the body.

Following the publication of a series of papers by Gautier (1899), claiming that amounts varying from 0·113 to 0·76 mg. per 100 g. were present in the normal mammary glands, thyroid gland, thymus gland, hair, skin and bones, and the denial of this claim by a Committee of the French Academy, wide controversy was aroused, particularly from the medico-legal experts, but as the result of a large series of examinations by Myers and Cornwall (1925) it appears to be generally agreed that such small amounts as those postulated by Gautier can be regarded as "normal". According to Glaister (1931)

" traces of arsenic less than one part per 5 million parts of viscera should be ignored ".

DISTRIBUTION AND STORAGE OF ABSORBED ARSENIC

About four-fifths of the amount of arsenic absorbed is stored and widely distributed in the tissues, including the liver, abdominal viscera, bone, skin, and particularly the hair and nails, where it may be detected many months after it has disappeared from the urine and faeces.

Determination of the rate of absorption of arsenic has been facilitated by the modern use of radioactive tracers. By exposing the hair to a flux of thermal neutrons, the arsenic is rendered radioactive, and its localization, as a fraction of length of the hair determined (Griffon and Darbaud, 1951). Arsenic was found in the hair in considerable amount in chemical workers manufacturing a solution of sodium arsenite (Hill and Faning, 1948)—108, 85 and 64 p.p.m. in 3 categories of exposed persons as compared with 13 p.p.m. in controls. Goldblatt and Goldblatt (1956) suggested that " a kind of equilibrium is reached in the hair which is independent of the amount of arsenic passing through the body as indicated by the markedly different urinary excretion ".

In a case of subacute poisoning of several weeks' duration, Heyndrickx (1955) found the greatest amount of arsenic in the proximal 5 cm. and from one-tenth to one-twentieth less in the more distal parts of the hair, a finding which he considered to suggest that the duration of the intake had been longer than the case history indicated.

The blood of normal women, according to Guthmann and Grass (1933), contains 20–100 μg. of arsenic per 100 g., and since they found a considerable increase during menstruation and the early months of pregnancy, they concluded that arsenic seems to have a direct relationship to growing tissue and cell proliferation. In women with carcinoma there was an average increase of 43 per cent over that of the intermenstrual normal value. In rats, about 80 per cent of the arsenic in the blood is concentrated in the red corpuscles.

Cows' milk contains amounts of arsenic varying between 32 and 60μg. per L. (Hove *et al.*, 1938).

EXCRETION

Arsenic is excreted slowly, some appearing in the urine and, to a smaller extent, in the faeces within 24 hours, but a large proportion of the amount absorbed is stored in the tissues and eliminated at varying intervals of time. The normal value of urinary arsenic for persons with no known exposure has been variously calculated as 0·014 mg. per L. (Webster, 1941); 0·017 mg. of As_2O_3 per 100 ml. (Watrous and McCaughey, 1945); and 0·13 mg. per L. (Pinto and McGill, 1953). According to Grollman (1958) there is practically no difference in the urinary arsenic content of adults and children.

The urinary arsenic of workers exposed to arsenic may show much higher values than non-exposed persons. Pinto and McGill found levels of an average of 0·82 mg. per L. as compared with 0·13 for the controls, but stated that evidence of systemic poisoning is rare even with a level of 4–5 mg. per L., indicating that much more arsenic can go through the human body without causing illness than has been previously realized. Orestano and Abbate (1937) believe that the amount of arsenic eliminated in the urine is independent of the dose so long as this is tolerated.

With regard to lead arsenate, it appears from the investigations of Fairhall *et al.* (1938, 1941, 1943) that this compound is broken down in the body with subsequent excretion of most of the arsenic by the kidney, and according to Gerin (1957) the arsenic disappears from the urine more rapidly than the lead. Fairhall's findings indicated furthermore that in the presence of lead, arsenic is eliminated more intensively and that the arsenate radical either decreases the absorption or increases the excretion of lead while soluble arsenates decrease the lead storage.

TOXICOLOGY

In acute poisoning arsenic is a general protoplasmic poison acting upon various ferment processes, especially the phosphatases (Oelkers, 1937), leading to diminished oxidation and tissue respiration. It has also a paralytic action on smooth muscle and thus acts as a vascular poison, leading to haemorrhage (Nonnenbruch *et al.*, 1936). In the cell, the toxic effect is exerted on the chromosomes, particularly—according to Bucher (1940)—as a blockage of the mitotic metaphase, a property which it shares with colchicum. It is believed by some authorities that the immediate effects on the gastro-intestinal mucous membrane are due to increased permeability of the capillaries.

In industry, acute poisoning from solid arsenic is rare; subacute and chronic poisoning usually arises from exposure to arsenic-containing dust and fume. The most dangerous arsenical compound, not used as such but occurring as the result of accident, is arsine, or hydrogen arsenite, a powerful haemolytic agent.

ARSENICAL POISONING IN ANIMALS

Acute.—A wide variation of toxicity has been reported in various animal species and even in strains of the same species; both the particle size and the amount of impurity have been found to influence the $L.D._{50}$ dose. From the investigations of Harrison *et al.* (1958) it appears that the strain variation is less marked in the mouse than in other animals. They also found that solutions of arsenic trioxide are many times more toxic than the dry powder, and that the high purity compound was less irritant to the gastro-intestinal tract than the crude sample, possibly on account of the presence of impurities such as antimony. Gastro-intestinal damage, as evidenced by severe convulsions and retching, and haemorrhage of the stomach and intestines was a marked feature of the crude arsenic trioxide, while the pure preparation caused much less discomfort and only slight reddening of the gastric mucosa. The ultimate $L.D._{100}$, however, was less for the pure than the crude preparation (39·4 mg. of arsenic per kg. as compared with 42·9). In the liver, fatty degeneration, cell necrosis and reparative changes following acute injury by arsenic have been observed (Rössing, 1941).

Arsenic trichloride ($AsCl_3$) a liquid evaporating with emission of dense white fumes, causes a severe conjunctival reaction with chemosis and necrotic corneal lesions (Uhde, 1946).

(c) *Arsine.* In a case reported by Dernehl, Stead and Nau (1944), intense irritation of the eyes, with palpebral oedema, occurred in a metal refinery where fume was accidentally generated. Arsine was thought to be the most active agent but stibine and sulphur hydrides were also present.

(d) *Organic Arsenicals.* The extreme toxicity to the eyes of some trivalent organic compounds is due, according to Duke Elder (1954) to their rapid linkage with the sulphydryl groups in proteins and enzymes essential for carbohydrate metabolism, a view also held by Dixon and Needham (1946). The most virulent is Lewisite (chlorovinyldichloroarsine), once intended but not used for chemical warfare.

Chronic.—The chronic symptoms observed in workers exposed to arsenic and its compounds are related chiefly to the skin, mucous membranes, gastro-intestinal and nervous systems, and in a few cases disorders of the circulatory system and the liver have been recorded. German observers have described many of these manifestations from the use of arsenic as an insecticide, particularly in wine dressers (Dorle and Ziegler, 1930; Schorndorff, 1938; von Pein, 1940; von Pein and Baurhenn, 1943) though it has been suggested that the arsenic poisoning of wine dressers is not due so much to inhalation or skin contact, but as the result of ingestion of contaminated wine.

The question of a potential carcinogenic action of arsenic on organs other than the skin has been much debated. The recorded cases of carcinoma of the lung, larynx, viscera, and multiple tumours of the skin or viscera, or both, associated with chronic absorption of arsenic are strongly suggestive of such a relationship, but some "adjuvant factor" in the metabolism or hormone balance of the sufferer or in the susceptibility of the affected tissues appears to be also concerned.

SYMPTOMS OF CHRONIC INDUSTRIAL POISONING

SKIN LESIONS

Lesions of the skin in association with industrial exposure to arsenic were described as long ago as 1728 by Henckel (the so-called Hütten-Krätze). During the nineteenth century many cases of erythematous, pustular, or even ulcerative or gangrenous lesions were described, chiefly from the manufacture or use of Schweinfurter Green but also of other arsenical materials.

Vigne (1930), describing the cutaneous lesions occurring during the manufacture of insecticides, considered that the most hazardous compounds in this respect were arsenic trioxide and Paris Green; sodium arsenite, however, has also been found potent in producing skin lesions of very varied character. Leoncini (1933) described ulceration of the hands and feet, scrotum and perineum from its use as a vermin killer, and Tamponi (1935) reported erythema, papules and ulcerations from its use as an insecticide.

The inorganic arsenical compounds have been regarded by the majority of observers as primary cutaneous irritants, not sensitizers. Schwartz *et al.*

(1947) classified arsenic disulphide, sodium arsenate and arsenite and potassium arsenate as primary irritants, but also designated arsenical compounds in general as "the principal sensitizers met with in industry". Holmquist (1951), while unable to express an opinion on the sensitizing capacity of every individual inorganic arsenical compound, found that the trioxide and pentoxide were definitely able to produce sensitivity; he considered that this capacity was shared to a large extent by other compounds of arsenic, the sensitization being dependent to some degree on the intensity of the exposure.

The question as to whether inorganic arsenical compounds can produce sensitivity to organic compounds has been discussed by Jones (1940). On the basis of two cases—workers in an arsenic mine, who showed skin reactions 11 years later following an injection of neoarsphenamine—Jones suggested that previous industrial poisoning may provide the mechanism for later sensitization to organic arsenicals.

Nature of the skin lesions.—*Acute and subacute dermatitis* is more common than the chronic or subchronic types. In the initial stages, which may arise in less than a week or only after years of employment, erythema, associated with burning and itching, is sometimes most intense around the follicles, giving the skin a spotted appearance; when occurring on the face, accompanied by swelling, this may disappear without further development or may be followed by *papular and vesicular eruptions.*

Pustular folliculitis may be accompanied by marked serous discharge, especially in areas exposed to rubbing or chafing, resulting in the formation of crusts. In some cases these lesions heal within a week leaving only slight pigmentation and desquamation; in others the skin becomes lichenified and liable to form new foci of inflammation even after cessation of exposure.

In the cases described in great detail by Holmquist (1951) where the exposure was related to the metallurgical working of copper ore in smelting works in Sweden, the dermatitis was mainly localized to the areas of greatest exposure—the face, neck, forearms, wrists and hands. It also occurred on the scrotum and thighs, the upper part of the chest and back and the lower legs. Recurrences in employees removed to departments with a lesser risk of exposure to arsenic suggested that some of the lesions were due to sensitization; this was supported by the results of patch tests, in which eczematous reactions were produced by arsenical compounds.

A less acute but very prominent feature of skin lesions due to arsenic is *hyperkeratosis*, often accompanied by hyperhidrosis, especially of the palms and soles. Under the name hyperkeratosis, Watrous and McCaughey (1945) included cracking skin, thickness and dryness of skin, and warts. A diffuse branny desquamation of the skin of the trunk and extremities with dark, deeply pigmented areas has also been described (Heyman *et al.*, 1956) and has been likened to that of Addison's disease.

A case of *arsenical melanosis* in a glass worker who also suffered from silicosis was described by Gilje (1951). In some areas the pigmentation alternated with depigmentation ("rain-drop" pigmentation); in others, especially the hands and feet, it showed a striped appearance. It was assumed that the inhaled silica-containing dust also contained arsenic. The

nature and causation of the melanosis has been investigated by several observers dating from Wyss (1890) and Gaus (1915) onwards.

Osborne (1925), summarizing his own findings and comparing them with those of the earlier observers, with whom he agreed on the whole, concluded that the pigment contained no arsenic but lipoids and melanin derived from cell metabolism, not from the " products of brokendown blood ", and that it arose chiefly in the corium and to a lesser extent in the epidermis, by an indirect action of arsenic on the mother substance of melanin.

Buchanan (1961) remarks that melanosis is certainly an indication of systemic absorption of arsenic, generally over a lengthy period, and not the result of local action.

The nails.—The presence of white striae in the fingernails, described by Mees (1919) has come to be regarded as almost a diagnostic accompaniment of arsenical polyneuritis. Mees observed this broad white band on all the fingernails of 3 cases of attempted murder or suicide by arsenic and stated that its presence in association with polyneuritis was confirmatory of the diagnosis of arsenical poisoning; it was still distinct long after the disappearance of arsenic from the urine. In the cases of Heyman *et al.* (1956), all of those who had had symptoms of arsenical intoxication for 6 weeks or more, showed this phenomenon; it was not present in 4 patients observed for less than that time. These authorities believe that an approximate estimation of the exposure to arsenic could be made from the distance of the lines from the base of the nail; but there was no evidence that the actual growth of the nail was retarded by arsenical neuropathy. In 1 patient the time of migration of the lines to the free edge of the nail was 5 months (the approximate time for the nail to grow from the matrix to the free edge in normal persons). Nevertheless, examination of 2 other patients with Mees' lines showed no arsenic in the hair or urine, indicating that these bands are not pathognomonic of arsenical intoxication.

Cancer of the skin.—The association of arsenic with skin cancer was reported by Hutchinson (1887), in relation to the internal administration of arsenic over long periods, and has been confirmed by many authorities since that time, especially from Fowler's solution (Arhelger and Krenen, 1951) and other arsenical medicinal preparations (Sommers and McManus, 1953). Skin cancer from external contact with arsenic-containing substances in industry has been relatively rarely reported; Leitch and Kennaway (1922), though they had succeeded in producing a typical squamous-cell carcinoma in animals by the external application of potassium arsenite in alcohol, stated that only two instances were on record up to that time which could reasonably be attributed to employment with arsenic ; both were workmen dealing with sheep dip.

In the series of cases of skin cancer recorded by Sommers and McManus (1953), most were associated with the medicinal use of arsenic; only 2 were occupational in origin. One of these had used lead arsenate during his work as an electroplater and had shown multiple keratoses of the hands for 5 years before biopsies of a lesion of the thumb showed hyperkeratosis and epithelial hyperplasia. Following amputation an invasive epidermoid carcinoma was found to be present.

Neubauer (1947) collected 143 published cases of arsenical epithelioma following medication with arsenic for diseases of the skin (psoriasis was predominant) and other conditions. The most common form was again Fowler's solution (potassium arsenite 1 per cent calculated as As_2O_3). Arsenic trioxide was also given as pills; Donovan's solution was a combination of the iodides of arsenic and mercury.

Nature of the carcinomatous lesions.—Among the varying types of arsenical cancer of the skin, epithelioma developing on the site of keratoses (the " Hutchinson type ") is the commonest. The keratotic lesions may have existed for many years before they begin to undergo malignant change to epithelioma, usually of the squamous type. Such lesions have also been recorded as developing in patches of psoriasis, and even in normal skin. The association of arsenic with multiple epitheliomatoses, sometimes of basal-cell type and of a low-grade malignancy, and with a chronic " precancerous dermatitis " (Bowen's disease), described by Bowen in 1912, is still under discussion by dermatologists.

MUCOUS MEMBRANES

Dermatitis of the face and eyelids is sometimes accompanied by conjunctivitis, with redness, swelling and pain. Two cases of severe keratoconjunctivitis were described by Paufique and Bonamour (1946) following exposure to calcium arsenate as an insecticide. In one case corneal anaesthesia was accompanied by a corneal ulcer. There may also be irritation of the nose and pharynx, causing acute or chronic rhinitis, and of the bronchial passages.

Perforation of the nasal septum was described by Davis (1917) and by Dunlap (1921) in workers employed in copper smelting. The actual perforation is in most cases preceded by slight epistaxis, some irritation of the nose, and the formation of crusts owing to the resultant obstruction to nasal breathing, pharyngitis and possibly low-grade laryngitis. The perforation develops from a white slightly elevated area about 5 mm. in diameter followed by necrosis on both sides of the septum, when the cartilage disappears from dystrophy. It was suggested by Dunlap that the arsenic-containing dust breathed into the nose and coming into contact with the moist membrane forms arsenious acid, which causes necrosis of the septal mucosa, and by Pinto and McGill (1953) who observed similar cases in their workers exposed to arsenic trioxide, that the large particles (over 5·5 μ) which form a substantial part of the dust, readily impinge on the septum.

GASTRO-INTESTINAL DISTURBANCE

True gastro-enteritis is not a common occurrence in industrial chronic arsenical poisoning. Pinto and McGill (1953) found only one case among their workers with arsenic trioxide, but digestive disturbance, as shown by nausea and vomiting, is occasionally reported. A case described by Mayers (1954) in which severe gastro-intestinal symptoms were predominant was unusual in that it apparently remained undiagnosed for more than 20 years in spite of numerous admissions to hospital for disorders suggestive of

arsenical poisoning. The man's exposure to arsenic in the form of Paris Green powder had been heavy and included the possibility of inhalation, ingestion, and skin absorption. The gastro-intestinal disturbance began soon after he started work, with acute colic and haematemesis. He was found to have a penetrating gastric ulcer which healed but returned when he resumed work and disappeared only when exposure ceased entirely. During his 20 years of more or less intermittent exposure he had repeated attacks of exfoliative dermatitis; these also disappeared when exposure ceased but left permanent trophic skin changes with discoloration. Other symptoms characteristic of arsenical poisoning were also present—conjunctivitis, upper respiratory irritation and polyneuritis—and death was finally due to cardio-vascular degeneration.

PERIPHERAL NEURITIS

The symptoms of peripheral neuritis following exposure to arsenical compounds in industry, though infrequent, are identical with those recorded as due to ingestion (Kelynack *et al.*, 1900) and others. Unlike the peripheral neuritis of lead poisoning, in which pain and disturbance of sensibility are usually absent, arsenical polyneuritis is accompanied by pain, with burning and tenderness in the affected limbs, and difficulty in walking. These symptoms were present in the cases described by Heyman *et al.* (1956), 7 of which were said to be due to direct contact with arsenate sprays or dusts. Some of the cases had an initial stage in which the symptoms were those of acute poisoning—nausea, vomiting and diarrhoea—but in the 7 industrial workers the onset was gradual, with development of sensory disturbances in the extremities—numbness, tingling and "pins and needles"—followed by severe symmetrical weakness in the feet and legs. As in the cases described by Hassin (1930), high levels of arsenic were found in the hair and also in the urine—2·5 mg. per 100 g. in the hair, and 0·1–6 mg. in a 24-hour specimen of urine. In Hassin's cases, where the source of the arsenical poisoning was not determined, the diagnosis was confirmed also by the presence of "Mees' lines" on the nails.

The difficulty in distinguishing between the polyneuritis of lead poisoning and that of arsenic is emphasized by a case recorded by Barbier *et al.* (1942). The polyneuritic symptoms were at first diagnosed as due to lead poisoning, since the man had used lead arsenate as an insecticide spray. The outstanding feature of this case was motor weakness of the hands and difficulty in walking; the diagnosis of arsenical polyneuritis rested chiefly on the evidence of an initial gastro-intestinal disturbance and the presence of Mees' bands on the nails; there was no hyperkeratosis and no tingling or numbness of the hands and feet.

THE LIVER

Involvement of the liver, with jaundice, sometimes ascites, was noted in early observations as a sequela of arsenical medication. Hutchinson (1887), for example, described liver injury resembling cirrhosis following arsenical treatment of chronic eczema. One of the first records of cirrhosis from the industrial use of arsenic was that of Dorle and Ziegler (1930) in wine dressers,

though, as already remarked, as in that of many successive observations on wine dressers in Germany, the ingestion of arsenic-contaminated wine is now believed to play a more important part than the actual exposure to the arsenical insecticides. Hurren and Heinlein (1943) stated that the increase in liver injury among employees in the wine industry since the introduction of arsenic spraying was to be largely attributed to the effect of arsenic, and that this injury was degenerative in character, reparable in some cases, but leading finally to cirrhosis. On the basis of the Takata-Ara reaction they found that 70 per cent of the workers examined showed a variable degree of liver injury though only 36 per cent showed a definite cirrhosis. In a fatal case with ascites a special feature was the presence of discrete parenchymal necrosis with reparative connective tissue formation. They conceded, however, that the influence of ingested alcohol could not be entirely excluded. This reservation applies also to the supplemental toxic action of nicotine, phosphorus and metabolic disturbance in similar observations by German authorities in the early years of this century.

DISORDERS OF THE HEART AND CIRCULATION

The subjective and clinical evidence for a primary cardiac injury in arsenic workers is not very definite, but the electrocardiograph has revealed abnormalities similar to those observed in animals fed on subtoxic amounts of arsenic (Butzengeiger, 1940 and 1949; Hadjoloff, 1940 and 1957).

Among 216 wine dressers using arsenical insecticides, Butzengeiger found 55, who showed other symptoms of chronic arsenical poisoning, to have an abnormal electrocardiogram indicating a toxic myocardial effect. Among these were 36 whose myocardial injury was severe, and some of them were suffering also from peripheral disturbances indicative of endo-angiitis—gangrene of the extremities, atrophic acrodermatitis and other less severe symptoms of peripheral damage. Butzengeiger described the endo-angiitis as indistinguishable from severe arteriosclerosis or endo-angiitis obliterans.

THE CARCINOGENIC ACTION OF ARSENIC

Examples of cancer of the skin in patients receiving arsenical medication and in arsenic workers having external contact with arsenical compounds have already been described, and there seems little doubt that carcinomas of the skin do arise especially on the sites of arsenical keratosis. The evidence for arsenical cancer of other organs is not so universally accepted, especially with regard to occupational exposure.

The view formerly held that the high incidence of lung cancer among the miners of Schneeberg and Joachimstal were due to arsenic has been more or less discarded in favour of radioactivity as the carcinogenic agent, partly because of the absence of characteristic arsenical skin changes. Hueper (1942) stated that "the possibility of a causal relation between the inhalation of arsenic dust and the development of pulmonary malignancy may be conceded but the probability of its relationship is small".

In a clinical and experimental study by Perry *et al.* (1948) among workers

in a factory manufacturing a solution of sodium arsenate, despite the previous finding by Hill and Faning (1948) in the same factory that on a statistical basis there was a greater tendency for arsenic workers to die of cancer than for other groups, radiographic examination did not reveal any case of bronchogenic carcinoma. More recent investigations by Roth (1956, 1957) and Braun (1958) do, however, show a definitely higher incidence among wine dressers in Germany. Roth found 10 cases of bronchial carcinoma among 30 workers with arsenical skin lesions. Braun, comparing the incidence of bronchial cancer in those suffering from arsenical dermatoses during the years 1951–1957 with that between 1939 and 1952 found a greatly increased incidence in the later years. Out of 16 of an average age of 52 years, all showing keratosis and some also melanosis, pre-malignant or malignant skin changes, 9 had inoperable bronchial carcinoma.

Tumours of other organs, most frequently in association with arsenical cancers of the skin, have also been described, notably by Sommers and McManus (1953) in their review of 18 cases of visceral cancer reported in various countries up to that year. Among these, of which only 5 were industrial workers, there were 7 cases of pulmonary tumour, 3 of the mouth and tongue, 3 of the ureter and bladder, 2 of the breast, 2 of the oesophagus, 1 of the stomach and 1 of the cervix uteri. Only 6 of these had associated cancer of the skin. In their own series of 27 cases, of which only 2 were occupational, many had not only multiple skin cancers, but also, among 6 who were submitted to autopsy, 4 had separate internal cancers of the bladder, prostate, oesophagus, colon, kidney and chest wall; in 3 cases the growths were multiple.

Roth (1956) also noted 5 cases of malignant liver tumour and one of oesophageal cancer associated with liver cirrhosis, and in Braun's series there was 1 case of carcinoma of the bile ducts also associated with cirrhosis of the liver, and 1 of a suspected sarcoma of the cervical lymph glands. Rosset (1958) has recorded a case of multiple internal carcinomas in a man who more than 20 years previously had used lead arsenate to spray potatoes, and had at that time developed keratotic lesions on the palms of his hands. The latent period of development of malignant tumours of possible arsenical origin is long—13–50 years according to Sommers and McManus (1953), 13–22 years in the experience of Roth (1956) and Braun (1958).

The most disputed point in the problem of the potential carcinogenicity of arsenic appears to be whether it is a direct agent, or whether it is dependent on other factors such as tissue susceptibility, skin sensitivity, photosensitivity, or other external or internal metabolic effects. On this point it does not seem possible at present to arrive at a direct conclusion. Even Goldblatt and Goldblatt (1956) in their admirable review of industrial carcinogenesis, and with their extremely wide experience of the subject, can only say that " the arsenical compound which produces no tumour in a workman is not a carcinogen for him until he, in a given tissue, brings about a meeting between a cell in the appropriate state and the compound in a sufficient concentration . . . *and* . . . from the very few cases of occupational arsenical cancer hitherto reported it may be considered that a combination of appropriate state and sufficient concentration is rare ".

ARSINE

Arsine (arseniuretted hydrogen; hydrogen arsenide; AsH_3) is not an industrial product in the economic sense, but an accidental evolution whenever nascent hydrogen is liberated in the proximity of trivalent arsenic.

PROPERTIES

Arsine is a colourless inflammable gas with a slight garlic-like odour, depositing arsenic on exposure to light and moisture (threshold limit value for an 8-hour working day, 0·05 p.p.m.). Concentrations of 3–10 p.p.m. will produce slight symptoms after several hours' exposure and 16–30 p.p.m. are dangerous according to Doig (1958).

OCCURRENCE

Since arsenic is present as a contaminant of many ores—zinc, lead, copper, antimony, gold, silver and tin—the formation of arsine occurs most frequently in the metallurgic industry, particularly from the action of acid on arsenic-bearing metal. It may also occur where the hydrogen ion is formed by hydrolysis, as in the reaction of moisture with calcium arsenide present as an impurity in ferrosilicon (Hake, 1910); in the process of wetting of aluminium and phosphate dross (Nau, 1948; Spolyar and Harger, 1950); in lead refining (Wills, 1948; Banik, 1956); and in the purification of tin (Macaulay and Stanley, 1956). In this last process reports from those of Legge (1924) onwards had previously recorded 30 cases of arsine poisoning with 12 deaths. Its occurrence has also been described during cyanide extraction of gold (Bulmer *et al.*, 1940); in the process of leaching of zinc (McKinstry and Hickes, 1957); very frequently in the cleaning out of furnaces and tanks (Wills, 1948; Hamilton and Hardy, 1949; Troisi, 1950); and even from mishandling of arsenical insecticides (Mohacek and Stajduhar, 1951).

TOXICOLOGY

The fatal effects of arsine were first reported in 1815, when Gehlen, a chemist, died from inhaling it in his laboratory. It is a powerful haemolytic poison with both acute and also chronic exposure. In the acute form the mortality rate is high. Muehlberger *et al.* (1928) stated that 20 per cent of 215 cases of poisoning occurring since 1815 had been fatal; Spolyar and Harger (1950) estimated a mortality of 12 among 30 cases recorded between 1923 and 1941, while during the years 1945–1946, 13 cases, 4 of them fatal—a mortality of 31 per cent—were recorded in the Annual Reports of the Chief Inspector of Factories.

ACUTE POISONING

The outstanding initial features of acute arsine poisoning are malaise, abdominal cramps, nausea and vomiting, and a red staining of the conjunctiva ; this pigmentation, according to Macaulay and Stanley (1956), is not

trifluoride (ClF_3), and bromine pentafluoride (BrF_5). The data do not suggest the existence of any fluoride-bearing degradation products which behave differently from fluoride ion. NF_3 and N_2F_4 intoxication resulted in persistently high concentrations of fluoride in erythrocytes. --Authors' abst.

280 REPEATED AND CONTINUOUS EXPOSURE OF LABROATORY ANIMALS TO ACROLEIN. J. P. Lyon, et al. *Toxicol. Appl. Pharmacol.* 17: 726-732, Nov. 1970

Experimental animals were repeatedly exposed to acrolein vapors 8 hr/day, 5 days/wk for 6 consecutive weeks in 2 studies at concentrations of 0.7 and 3.7 ppm. Four continuous exposures to acrolein were conducted 24 hr/day for 90 days at concentrations of 0.21, 0.23, 1.0, and 1.8 ppm. Each experimental group of animals contained rats, guinea pigs, monkeys, and dogs. The animals were observed for toxic signs, mortality, and weight changes, and hematologic, biochemical, pathologic, and histopathologic examinations were made on the surviving animals. In both of the lower-level continuous exposures and in the 0.7 ppm repeated exposure, the animals appeared normal throughout the studies and gained weight. In the higher-level continuous exposures and the 3.7 ppm repeated study, the dogs and monkeys were visibly affected, and abnormal weight patterns were observed in some animals. The data from repeated studies support the current Threshold Limit Value (TLV) of 0.1 ppm. A tentative 90-day Confined Space Guideline (CSG) of 0.02 ppm is suggested based on data obtained from these studies. --Authors' abst.

281 ARSENIC AND WATER POLLUTION HAZARD. E. S. Pattison. *Science* 170: 870, Nov. 20, 1970

Undue speculation in the press, scare headlines, and the drawing of widesweeping conclusions about alleged hazards to consumers have resulted from the report by Angino et al. (Science 168: 389 (1970). Under no circumstances (whether examining raw and treated sewage. raw and treated drinking water, and river water) were Angino et al. able to present data that indicated that arsenic concentrations remotely approached those that would disqualify these waters as water supplies. Moreover, finding traces of arsenic in wash water (which is certainly not recommended for drinking, in any case) likewise does not constitute a threat. Angino et al. made no apparent effort to evaluate the impact of the use of farm insecticides (arsenicals) or industrial and municipal discharges on the one river they studied (the Kansas River). In fact, all they demonstrated was that arsenic, in trace quantities, is a ubiquitous material found widely in nature and that it does not constitute a hazard to water quality at the concentrations they reported. --Cond. from text

282 THE ARSINE HAZARD. Anon. *Lancet* 1: 71-72, Jan. 9, 1971

Arsine poisoning, within or without industry, is rare, which is fortunate since arsine (arseniuretted hydrogen) is one of the most poisonous of industrial fumes. Until lately, the prognosis of severe poisoning was grave. It is not produced intentionally in industry, for it has no commercial use; so poisoning results from the chance contact of nascent hydrogen and arsenic, or the watering of an arsenide. Greater awareness by the industries concerned of the dangers of chance arsine evolution has undoubtedly prevented accidents. Improvements in exclusion of arsenic as an unwanted contaminant in industrial processes have worked to the same end: for example, modern production methods produce an arsenic-free sulphuric acid. The possibility has been raised of the missed mild case of arsine poisoning. Mild poisoning unaccompanied by oliguria may remain unrecognized and should be considered in the diagnosis of hematuria or jaundice in a patient whose occupation brings him into contact with acids and metal. --Cond. from text

47 Distribution of Se-75 in Serum Proteins of Chicks and Influence of Selenium on Albumin Recovery. E. D. Walter, L. S. Jensen and J. S. Dunlap. Proc. Soc. Expll. Biol. Med. 114, 527-530 (Nov. 1963).

Se-75 was orally administered to 3-week-old chicks fed either selenium deficient or supplemented diets. Distribution of Se-75 in serum proteins with time and its effect on serum protein pattern were determined electrophoretically. Selenium in the diet had no effect on the distribution of Se-75 in the protein fraction, but markedly decreased its retention. After 2 hours the major portion of the dose was found in the beta and gamma fraction and the activity in this fraction increased with time. Marked increases in A/G ratios in depleted chicks were observed within 96 hours after administration of Se-75. Albumin was increased and globulin fractions were decreased. Increases in A/G ratios, somewhat smaller in magnitude, were also noted in chicks receiving a diet supplemented with selenium. -- Authors' summary

48 Effect of Arsenic Trioxide Exposure on Mortality. S. S. Pinto and B. M. Bennett. Arch. Environmental Health 7, 583-591 (Nov. 1963).

A study has been made in a copper smelter of the causes of death among present and pensioned employees dying in the period 1946-1960. The influence of arsenic trioxide exposure was specifically reviewed. Previous work had shown men in this plant not exposed to arsenic excreted an average of 0.13 mg. arsenic/liter urine; those exposed excreted an average of 0.82 mg. arsenic/liter urine. There was no evidence that chronic arsenic trioxide exposure of the amount described in this study is a cause of systemic cancer in humans. Industrial arsenic trioxide exposure of the amount described in this study had no measurable effect on fatal cardiovascular disease. Thirty-six references are given. -- Authors' summary

49 Some Problems in the Large Scale Handling of Beryllium. F. B. Crossley. Ann. Occ. Hyg. (London) 6, 89-103 (April-June 1963).

A highly technical description is given of the beryllium pilot plant at ICI Metals Division at Birmingham. The maximum permissible concentrations are: (a) in the process area, (1) over any 8-hour period, 2 micrograms/cu.m. in the breathing zone, (2) the daily average must be within this limit but for any 30 minutes must not exceed 25 micrograms/cu.m.; (b) outside the process area concentrations must not exceed 0.01 microgram/cu.m. averaged over a month, calculated with reference to the breathing zone. This is observed by stack monitoring. Before the plant started working, measurements of beryllium air levels made in the Birmingham area were well above the tolerance level. Control of the beryllium dust content of the air in the plant is achieved by ventilation techniques which are described in detail. The control of the personnel in the areas where beryllium is worked is obtained by pre-employment examination with x-ray examination, and subsequently at intervals of 6 months. The provision of special clothing and of cleaning facilities and the use of masks and air-fed pressure suits are described in detail. -- Bull. Hyg.

50 Delayed Carcinoma from Beryllium Aerosol in Man. H. K. Niemöller. Intern. Arch. Gewerbepathol. Gewerbehyg. 20, 180-186 (1963). German.

Various authors have reported the production of malignant tumors in animals after exposure to beryllium salts. The present paper presents 3 cases which confirm for man the results obtained by Schepers in animals. The first patient had come into contact with beryllium compounds in the form of dust, fumes, or gas at work for a period of 3 years. From 1943, he had no further exposure. In 1946, his chest x-ray showed an appearance interpreted as due to beryllium; he was given a pension. In 1959, he developed a cancer of the lung and died of intracranial pressure due to cerebral metastases in 1960. The lungs did not show the typical beryllium granulomata but there was a diffuse fibrosis. The lung tissue on spectrum analysis gave a positive finding for beryllium. This may be the first case in world literature described as a late beryllium carcinoma. The second patient was employed for 15 years in a beryllium factory and at the end of that time in 1945 was found to have typical signs. In 1961, an increased shadow on the right side of the mediastinum was investigated. Cells of a squamous celled carcinoma were

142 Physical and Psychologic Factors in Glue Sniffing. O. N. Massengale, et al. New Engl. J. Med. 269, 1340-1344 (Dec. 19, 1963).

Twenty-seven children who were chronically habituated to inhalation of cement vapors were seen in the Adolescent Clinic. No physical or laboratory abnormalities directly attributable to contact with glue were detected. Personality patterns in this group of children were remarkably similar. Toluene was found to be the major volatile component of commonly used cements subjected to gas chromatographic analysis. Available information regarding the toxicity of this compound when inhaled is conflicting. Although glue sniffing appears to be physically harmless to most children, it is an increasingly prominent stimulus to delinquency. The authors list 26 references. -- Authors' summary

143 Evaluation of Fluctuating Carbon Monoxide Exposures. J. R. Goldsmith, J. Terzaghi and J. D. Hackney. Arch. Environmental Health 7, 647-663 (Dec. 1963).

The agent, carbon monoxide, was shown to fluctuate over time and place. This is a major factor in effects of exposures of human populations. The patterns of population exposure must include the exposure of cigarette smokers, of those subjected to community air pollution, those with exposures to motor vehicle exhaust during commuting, and those with occupational exposure to carbon monoxide. A reasonable division of the population in a community was shown to consist of 6 different categories. Another important population variable consists of those unusually sensitive to impaired oxygen transport because of age or medical status. The mechanism of action is predominantly the impairment of the oxygen transport function of the blood. Other possible mechanisms were discussed. A mathematical approach for predicting the time course of carboxyhemoglobin, given the temporal fluctuation of carbon monoxide was derived. These mathematical expressions required some simplifying assumptions. The expressions were used to develop a computer program, and, with a simulated set of sinusoidal exposure data, the expected carboxyhemoglobin was calculated by using a method of interative integration. Several sets of experimental data were approximated by both analog and digital computer techniques. The possible synergistic effect of other pollutants was reviewed. -- Authors' summary

144 Carcinogenesis Tests of Two Inorganic Arsenicals. C. Baroni, G. J. van Esch and U. Saffiotti. Arch. Environmental Health 7, 668-674 (Dec. 1963).

Arsenic trioxide was tested by oral administration and sodium arsenate by skin application on Swiss mice. Each compound was tested in 3 ways: (1) alone (carcinogenesis test); (2) in combination with skin applications of the promoting agent croton oil (test for initiating action); and (3) after initiation with a single skin application of 7,12-dimethylbenz(a)anthracene or with administration of urethan by stomach tube (test for promoting action). Control groups were studied concurrently. All tests failed to show any carcinogenic, initiating, or promoting activity of the 2 arsenicals under the experimental conditions used. In view of available evidence indicating that certain exposures to arsenic represent a human cancer hazard, further studies on the role of arsenic in carcinogenesis are considered necessary. There are 25 references. -- Authors' summary

145 The Fate of Cd-109 in the Mouse. An Autoradiographic Study After a Single Intravenous Injection of Cd-109 Cl_2. M. Berlin and S. Ullberg. Arch. Environmental Health 7, 686-693 (Dec. 1963).

The body distribution of cadmium in mice killed at various times, from 5 minutes to 16 days, after a single intravenous dose of 8 microcuries Cd-109 Cl_2, carrier free, was studied by autoradiography of sagittal whole-body sections. The relative order of concentrations found in the organs of the body was estimated by densitometry. The distribution is described in detail. The autoradiograms indicated excretion of cadmium by gastric and colonic mucosa and in the bile. Very little elimination of cadmium, however, was found to occur during the 16 days of observation. Cadmium concentration was seen to decrease only in the mucosa of the intestinal tract, where it fell rapidly after 24 hours. Considerable amounts of cadmium were demonstrated for the first time in the interstitial tissue of the testes and in the posterior and anterior lobe of the hypophysis. A distinctive pattern of localization in the renal cortex was also found, indicating selective accumulation in special structures. -- Authors' summary

375 Burn Therapy: V. Disaster Management—To Treat or Not to Treat? Who Should Receive Intravenous Fluids? A. W. Phillips. Ann. Surg. 168, 986-996 (Dec., 1968).

In a disaster, when there are more burn casualties than can be cared for by the available personnel or when medical supplies are limited, a knowledge of the probabilities of survival for patients of varying ages with varying burn extents will aid in achieving the maximum number of survivals. A helpful rule is the Adult Rule of 90, worked out from actual burn statistics. Adults whose age plus burn extent exceeds 90 have less than a 50:50 chance of survival. If everyone cannot be treated, these should be among the first for whom palliative management is considered. If the situation improves this rule can be softened to 100 or, if supplies and personnel are still insufficient, it can be dropped to 70. Conventional treatment should be resumed at the earliest possible opportunity. If this rule had been used on 932 consecutively admitted burned adults at the Massachusetts General Hospital, only 12 who actually survived would have been denied fluids. At the cost of those 12 lives, 1,000 liters of fluid would have been saved, enough to treat 60 adults or 120 children in whom it might spell the difference between life and death.
--J. Am. Med. Assn. References & Reviews

376 Intravenous Glucose Tolerance, Insulin, and Free Fatty Acid Levels in Burn Patients. S. P. Allison, P. Hinton, and M. J. Chamberlain. Lancet 2, 1113-1116 (Nov. 23, 1968).

Intravenous glucose tolerance tests performed during the shock phase of burn injury and repeated one to four weeks later show that in the shock phase there is glucose intolerance, a high level of free fatty acids, and failure of the plasma immunoreactive insulin level to rise in response to intravenous glucose. These changes were related to the severity of the burn; they may be due to the high level of epinephrine secretion found in such patients. In the later phase there were higher than normal blood levels of fasting insulin and of insulin response to glucose, suggesting insulin resistance. Burn patients should be put on a high-carbohydrate regimen in the form of glucose and insulin or of fructose. --J. Am. Med. Assn. References & Reviews

377 Magnesium Deficiency Syndrome in Burns. A. Broughton, I. R. M. Anderson, and C. H. Bowden. Lancet 2, 1156-1158 (Nov. 30, 1968).

Twenty patients with burns were investigated for the magnesium deficiency syndrome. Eight showed a significant fall of serum magnesium, and five of these had symptoms of magnesium deficiency. Some of the psychiatric symptoms exhibited by many burned patients may be due to or aggravated by magnesium deficiency. --J. Am. Med. Assn. References & Reviews

378 The Effect of Ingested Arsenic on Methylcholanthrene-Induced Skin Tumors in Mice. J. E. Milner. Arch. Environmental Health 18, 7-11 (Jan., 1969).

Three strains of mice (C X C3H, DBA, and Balb/C) were selected on the basis of differing vigor or potentiality for cutaneous tumor development or both. These animals were fed arsenic trioxide in their drinking water in a concentration of 0.01%. Cutaneous tumors were initiated by the topical application of methylcholanthrene disks and promoted by transplantation. Although arsenic treatment appeared to increase the number of papillomas produced in the DBA strain, the effect was not statistically significant. The C X C3H mice, however, displayed an opposite effect, in that arsenic treatment resulted in a decrease in the number of papillomas produced. This effect was statistically significant with a P value <0.05. There are 20 references.
--Author's abst.

CHEMICAL HAZARDS

379 Teratogenic Effect of Cadmium and Its Inhibition by Zinc. V. H. Ferm and S. J. Carpenter. Nature 216, 1123 (Dec. 16, 1967).

Pregnant hamsters were injected intravenously on the eighth day of gestation with either 2 mg./kg of cadmium sulfate, 2 mg./kg of zinc sulfate, or a mixture of 2 mg./kg cadmium sufate plus 2 mg./kg zinc sulfate. Zinc alone provoked a very mild teratogenic response. In identical conditions, cadmium caused a marked embryocidal and teratogenic effect; approximately 66%

CHRONISCHER SCHADIGUNGEN DURCH UMWELTVERUNREINIGUNGEN - Lachnit V. - Kolingasse 10, Wien - WIENMED.WSCHR. 1972 122/4 (43-49)

Substances which may on occupational exposure at fairly high concentrations cause disease or damage health are discussed. Of the many trace elements in inhaled air most are present in such small quantities that damage to health is hardly likely, even in the vicinity of industrial plants etc. Certain metals such as nickel and cadmium merit greater attention in the future, however. Despite their low atmospheric concentration, socalled neighborhood cases have already been reported. Lead is one of the commonest and most severe atmospheric pollutants. Pollution by lead has been largely contributed to by the use of petrol containing lead. Longterm studies show that the maximum allowable concentration of lead may reduce the life expectancy of laboratory animals. A toxicological effect is also suggested by the reduced activity of ALA dehydratase observed at such lead levels. This may be interpreted as an early sign of the effect of lead on this enzyme, important in synthesis of heme. To prevent further increase of lead levels in the nonoccupationally exposed population a rigorous reduction or elimination of the lead content in petrol should be enforced. Some air pollutants have decreased recently in some countries, due to legal action; this has not occurred with asbestos fibers, which are extremely dangerous. The presence of socalled asbestos bodies in the lungs of nonoccupationally exposed people indicates the necessity of further studies. Whether these bodies which give a positive reaction for iron are indeed for the major part asbestos bodies can only be decided by comparative serial investigations. Poisoning with organic mercury compounds resulting from consumption of mercury polluted fish has occurred not only in Japan (Minimata disease) but also in Scandinavia and Canada. This has led to an investigation of the metabolism of these substances. Organic mercury compounds, especially methyl Hg compounds, have a particular affinity for the central nervous system. Determination of mercury in plasma or urine in cases of poisoning by these compounds yielded quite low Hg levels, though in whole blood or organs the level was much higher. For this reason mass poisonings have frequently been interpreted incorrectly. Prevention must consist of prepurification of waste water of the appropriate industrial plants.

423. Health aspects of nitrates in drinking water - DEVELOPMENTS IN WATER QUALITY RESEARCH - Gruener N. and Shuval H.I. - ANN ARBOR SCI.PUBL. 1970 (89-90)

The danger of water contamination by nitrate salts is dealt with in this article. Recent developments have created the need to embark on a study to determine if present nitrate concentrations in drinking water are having any detrimental effects on the population exposed. In addition, the authors felt that a basic reevaluation of the nitrate standard in drinking water was called for, since this standard was originally based on very limited toxicological and epidemiological information and has been subject to criticism for some years. Of particular concern has been the suspicion that a form of subclinical chronic methemoglobinemia might exist in infants in those areas with moderately high nitrate concentrations in drinking water. Consequently, the present state of knowledge concerning nitrate methemoglobinemia is also reviewed.

424. Health aspects of arsenical in the environment - Lisella F.S., Long K.R. and Scott H.G. - Dept. Prev. Med. Environm. Hlth, Coll. Med., Univ. Iowa, Iowa City, Ia. 52240 - JENVIRONM.HLTH 1972 34/5 (511-518)

In a literature review on arsenical compounds, this paper points out the possible hazards to human health and the environment resulting from their use. The major headings of this review include: the contemporary uses of arsenicals, illness and death associated with arsenic, arsenicals in the environment, and analytical procedures for the detection of arsenic.

425. Role of cadmium in human and experimental hypertension - Thind G.S. - Dept. Med., Sch. Med., Univ. Pennsylvania, Philadelphia, Pa. 19146 - JAIR POLLCONTROL ASS. 1972 22/4 (267-270)

Acute and chronic studies performed in the authors' laboratory in normal rabbits, dogs, human control subjects, and patients with hypertension are reviewed. Cadmium, a common contaminant of air, water, and food, produces persistant hypertension in the rabbit and dog. The pervasive metal is predominantly deposited in the kidney and liver, and to a lesser extent in the blood vessels of the cadmium hypertensive rabbits. Vascular responsiveness to angiotensin in the cadmium hypertensive aortic strips was significantly lower than that of the strips obtained from control normotensive rabbits. Cadmium hypertensive aortic strips also developed significantly lower passive tension on step wise increase in the original length of the strips (strain). Administration of cadmium acetate directly into the renal artery, preceding the injection of the vasopressor (angiotensin, epinephrine or norepinephrine), resulted in a dose related reversible inhibition of the vasopressor induced renal vasoconstriction. It is probable that significant pathophysiological changes in experimental cadmium hypertension would occur in the vascular system and the kidney, where cadmium deposition was the greatest. Mean plasma cadmium levels were significantly higher in patients with hypertension. Plasma zinc levels, however, were significantly lower only in hypertensive patients with renovascular and renal parenchymal disease but not in essential hypertension patients. A program of detailed epidemiological studies and public health measures is needed for further definition of the role of cadmium in idiopathic human hypertension.

426. Alkyl mercury poisoning in humans. Report of an outbreak - Pierce P.E., Thompson J.F., Likosky W.H. et al. - 845 Central Ave, Albany, N.Y. 12206 - JAMERMEDASS 1972 220/11 (1439-1442)

Three members of a family of nine that ingested mercury contaminated pork became ill

so they have vaccinated council staff against influenza in the autumn. It has not been possible accurately to assess the value of the procedure, but last winter's figures are of some interest though the number are small. Difficulties arose in obtaining vaccine against the Hong Kong strain in the autumn of 1968, and a monovalent vaccine did not arrive until January 1969. As the expected epidemic had not yet materialized it was decided to vaccinate those who were willing. In the autumn of 1969 vaccination again was offered with a bivalent vaccine. In the first 25 vaccinated persons there was an unduly high proportion complaining of minor side effects, and the dose for the remaining 87 was reduced from 1 ml. to 0.5-0.75 ml., and no further trouble was experienced. During the period 16 December 1969 to 27 January 1960 an outbreak of influenza occurred as part of the national epidemic with a peak locally in early January, when claims for sick benefit reached a weekly figure of approximately 450% above the seasonal average. Strains of tha Hong Kong variant of influenza virus A2 were isolated in the area. Returns from councils of absence owing to illness, believed to be influenza, during December and January were as follows: Unvaccinated 164, off sick 41; vaccinated once only 27, off sick 7; vaccinated twice 85, off sick nil. From this it will be seen that there is no difference in the absentee rate of those who were unvaccinated from those who received one dose only in November 1969. In the case of those who received two doses there were no absences, and this is statistically significant. Although one cannot draw any firm conclusion because of the small number who received one dose only, and in 23 a reduced dose, the authors think it seems prudent to advise an initial course of two doses in the previously unvaccinated and where there has been a significant change in the strain of the A2 virus.

15. CARCINOGENESIS

921. World maps of cancer mortality rates and frequency ratios. Parts III and IV (conclusion) - Dunham L.J. and Bailar III J.C. - Nat. Cancer Inst., Bethesda, Md. - INDUSTRMEDSURG. 1970 39/6 (37-53)

This is a continuation of a series which includes 16 maps of cancer mortality ratios and frequency rates, based on a review of cancer data by geographic areas. More than 100 such areas are included. The data are recorded on maps for the following cancers in males: oral cavity and pharynx, esophagus, stomach, intestines and rectum, liver, larynx, lung, and bronchus, prostate, urinary bladder, and leukemia. Data for females are given for the following sites of cancer: oral cavity and pharynx, esophagus, intestines and rectum, breast, and uterine cervix. The data are arranged in sequence by International List numbers, with males placed before females where both sexes are included. The present publication is adapted from a longer article published in the Journal of the National Cancer Institute, Vol. 41.

922. Nasal cancer in woodworkers - LANCET 1970 2/7666 (253)

Editorial. Brief review of recent literature on this problem.

923. Carcinoma of pancreas due to effect of arsenic in a self employed farmer and vineyard tender - PANKREAS CA DURCH ARSENEINWIRKUNG BEI EINEM SELBSTANDIGEN LANDWIRT UND WEINGARTNER - Finzel L. - Dienstst., Staatl. Gewerbearztes Gewerbeaufsichtsamt, Heilbronn - ARBEITSMEDSOZIALMEDARBEITSHYG. 1970 5/9 (251-252)

During the years 1937 to 1939 a farmer had used (6 times per year) an arsenical insecticide. He developed warts, and in 1951 a skin carcinoma had to be excised. Lymph node metastases developed. He was under continuous treatment for cancer of the right side of the head and neck up to 1962. In 1966 jaundice developed, and he died in 1967. At autopsy a carcinoma of the pancreas was found. A relation between his disease(s) and his former occupational activities was accepted by the insurance company.

924. The future and lung cancer - Haddow A.J. - HEALTH (Lond) 1970 7/2 (23-25)

The impact of lung cancer on the population has changed enormously during this century and, to appraise what the future may bring, it is necessary to outline the events of the last few decades and the present position. Death rate from lung cancer is increasing. There is reason to anticipate that the rate in males will continue to increase for a number of years, and that mortality in women will soon begin to increase much more rapidly. In other words, it is believed that in the near future we shall face a much worse situation than at present. The age factor, and the role played by cigarette smoking are mentioned. The smoking habits and lung cancer mortality of women are 20 yr in arrears of the men and, if the present trend continues, they could, in the next 20 yr, reach the male mortality level. Smoking in men is still increasing, but not as rapidly as formerly; in women it is increasing very rapidly. Air pollution is not a major factor. Unless tobacco consumption can be checked, little can be done. The situation will almost certainly deteriorate further as smoking during school days is looked on more leniently today, with the result that more children leave school already confirmed and often heavy smokers. As the latent period seems to be between 15 and 20 yr, it may be expected that lung cancer cases among people in their thirties will be seen.

16. LABOR AND MORBIDITY

16.1. Circulatory system

925. Exercise and hypnotherapy in the rehabilitation of the coronary patient - Kavanagh T., Shephard R.J., Pandit V. and Doney H. - Rehab. Cent., Toronto - ARCHPHYSMED. 1970 51/10 (578-587)

A comparison was made of 2 rehabilitation programs for patients after coronary occlusion. The first consisted of progressive physcial exercise under the supervision of a physician and

1093 Methemoglobinemia Caused by Spinach Containing Nitrites: Preliminary Report. A. Sinios. Munch. med. Wochschr. 106, 1180 (June 26, 1964).

A gray, livid color was observed in three infants, 3 and 4 months of age, from one to two hours after they had been fed spinach. Until then the infants had been well. The livid coloration was accompanied by tachycardia. The blood was chocolate brown, and a spectroscopic examination revealed methemoglobin. Large amounts of nitrite were detected in left-overs of the spinach fed to two of the infants, and the spinach found in gastric washings of the third infant contained some nitrite. Feedings with the same spinach puree had caused no symptoms on the day before. The spinach had been stored at room temperature. The author reasons that the nitrite must have derived from the multiplication of nitrite-forming bacteria in a spinach puree which contained nitrates, so that the nitrate was converted into nitrite. Studies have been started which suggest that this explanation is correct. The great sensitivity of young infants to toxins forming methemoglobin has been proved earlier by methemoglobinemia developing in infants whose formulas had been prepared with well waters containing nitrates.
-- J. Am. Med. Assn. References & Reveiws

1094 Investigation of SO_2 Effects on Rubber Trees as a Means of Forestalling Injury to Malayan Plantations from Refinery Emissions. Eileen Brennan, Ida A. Leone, and R.H. Daines. J. Air Poll. Control Assn. 14, 229-233 (June, 1964).

Four-hour fumigations of dry rubber trees under conditions simulating the climate of Malaya did not produce injury until the concentration of 0.78 SO_2 ppm was reached. Fifteen-minute exposures of the trees failed to cause injury until the concentration of 75 to 100 ppm SO_2 was reached. When rubber plants having wet leaves were fumigated for a 4-hour period, slight injury was produced at 0.40 ppm SO_2. Total sulfur determinations of composite dry leaves showed no significant increase over than in untreated checks until the concentration of 0.70 ppm SO_2 was reached. Trees which were fumigated wet showed a significant increase in total sulfur content over dry check trees even at the lowest SO_2 concentration of 0.13 ppm. Old leaves consistently had a higher total sulfur content than did younger leaves. In young leaves a considerable part of the absorbed sulfur (up to 30%) could be washed off the surface, whereas old leaves or composite samples failed to show any decrease in sulfur content on washing. This might be used as a criterion for exposure of foilage to atmospheric SO_2. A 3 week fumigation at 0.30 ppm SO_2, the maximum concentration predicted by Esso engineers in the Port Dickson area, failed to produce any injury symptoms. A total sulfur content of the foilage sufficient to cause injury when accumulated at a rapid rate failed to injure when accumulated over a 3 week period. Respiration studies failed to indicate the possibility of hidden injury occurring during this prolonged fumigation. Rubber trees respond similarly to other woody species to the presence of SO_2, being injured at much higher concentrations than were most of the herbaceous species tested.
-- Authors' summary

1095 Arsenic Induced Carcinoma of the Skin and Lung. G.C. Hill. Penna. Med. J. 67, 35-38 (Sept. 1964).

It has been known for more than 75 years that inorganic arsenic in its trivalent form is a potent carcinogenic agent. Since Hutchinson (Brit. Med. J. 2, 1280 (1887)) reported the association of arsenical keratoses with carcinoma of the skin, there have been many cases reported of arsenical keratoses. Subsequently, relationship to multiple cancers of the skin was more significant and keratoses became important as evidences of early malignancies. Exposure to arsenic is not only associated with an increased incidence of multiple cutaneous carcinomas, but with increased frequency of carcinomas of internal organs as well. The present case of a 47-year-old male is presented as an example of a patient in whom dermatitis herpetiformis was treated with oral Fowler's solution and in whom subsequently developed the typical arsenical dermatoses, Bowen's disease of the skin, cutaneous squamous cell carcinoma, and carcinoma of the lung. The long-latent interval of carcinogenic action of arsenicals was manifested in this case by appearance of cutaneous carcinoma approximately 20 years after known ingestion of arsenic in the form of Fowler's solution. A long-latent period, however, is not necessary for all patients, as according to Rosset, many patients with psoriasis have been taking Fowler's solution for over 30 years, while some cases have demonstrated malignancy after a short period

of therapy and after ingesting varying amounts of the drug. Arsenic induced carcinoma of the skin and internal organs continues to occur despite almost a centrury-old knowledge of the neoplastic inducing properties of arsenic. This is probably one of the few malignancies which can be almost completely prevented, yet, exposure in the form of medically prescribed drugs, multiple occupational uses, and the ever increasing content of arsenic in American cigarettes continues.

1096 Serum Aspartate and Alanine Transaminase Levels in Workers Exposed to Lead. H.A. Waldron. J. Clin Pathol. 17, 149 (March, 1964).

Serum aspartate and alanine transaminase levels were studied in a group of 46 workers exposed to lead. In none of them did the level of either enzyme vary from the values found in a group of 50 healthy persons with no industrial exposure to lead. No correlation was found between levels as aspartate transaminase or alanine transaminase and blood lead concentrations. -- Public Health Eng. Absts.

1097 Exposure to Aromatic Hydrocarbons in a Coke Oven By-Product Plant. E.B. Hay,III. Am. Ind. Hyg. Assn. J. 25, 386-391 (July-August, 1964).

This paper presents a study of aromatic hydrocarbon (benzene, toluene, and xylene) exposure in a coke oven by-product plant of an integrated steel mill. Three commercial aromatic hydrocarbon detector kits were used concurrently and evaluated for field use. The accuracy of each detector was determined by a comparison with results obtained by collecting the air-borne aromatic hydrocarbons in a silica gel absorption apparatus and subsequent laboratory analysis. The ratio of inorganic to total sulfate in the urine was utilized as a biological index of exposure, and the results were compared with time weighted average concentrations to which the individuals were exposed. The study showed no excessive aromatic hydrocarbon exposure to employees in this plant. -- Author's abst.

1098 Methane Diisocyanate: A Respiratory Hazard? E.O. Longley. Arch. Environmental Health 8, 898 (June, 1964).

As the search of the literature disclosed no references to the development of respiratory symptoms following exposure to methane diisocyanate (MDI), the author reports an incident which may indicate the need for caution when using this material. MDI was applied as a rigid foam insulation to the inside of a railway carriage standing inside the main doors of a carriage workshop. The team applying the MDI wore full protective clothing and air supply respirators. A gentle breeze carried mist from the overspray into the interior of the workshop. Despite the fact that 12 employees working in the workshop moved to points 60-120 feet from the spraying area, all of these employees developed symptoms, the onset of which varied from an hour to several hours after exposure. Of the 12 men, 7 developed asthmatic breathing, 11 experienced retrosternal soreness, 12 noticed a constriction of the chest, 10 had a cough which in most cases was paroxysmal and in a few cases, persisted for 7-10 days. Two men noticed a pain behind the eyes, one was "depressed" for 24 hours, 2 suffered headache, 2 had nasal discharge, and one had insomnia on the evening of exposure. The men wearing respirators while spraying were unaffected. The occurrence of symptoms in the 12 men, following immediately upon exposure to the mist from MDI would suggest that toxic levels of MDI can be expected when a spraying technique is employed.

1099 Respiratory Exposure of Volunteers to Parathion. W.V. Hartwell, et al. Arch. Environmental Health 8, 820-825 (June, 1964).

Although toxicants generally are believed to be more dangerous when ingested or inhaled, most reports assessing the hazards from occupational exposure to parathion suggest that the majority of occupational accidents are due principally to dermal exposure. Previous observations of the authors indicated that some individuals could sustain massive discrete dermal exposure to parathion without clinical evidence of poisoning or significant depression of

990 Multiple Carcinomata Following Ingestion of Medicinal Arsenic. S. Minkowitz. Ann. Internal Med. 61, 296-299 (Aug. 1964).

A 21-year-old white male was admitted to the Kings County Hospital Center in 1947, because of a painless ulcer of his tongue that had first been noticed 6 weeks earlier. Past history revealed that he had had Sydenham's chorea between the ages of 7 and 16 and that he had taken 10 minims of undiluted Fowler's solution (1%, calculated as AS_2O_3) daily between the ages of 7 and 10 on the advice of his family physician; a total dose of 7.8 g. of AS_2O_3 as Fowler's solution over a 3-year period during his childhood. He finally bore about 3 dozen warty lesions scattered over the entire body. Many were present on the palms, soles, and trunk. Nine of his lesions were found to be individual primary epidermoid carcinomata. Two of these arose on mucosal surfaces. Seven of the biopsied lesions contained foci of Bowen's disease and one had the histologic characteristics of a keratoacanthoma. Fowler's solution, extensively used for innumerable disorders in the past, has been the medicinal form of arsenic most frequently incriminated in carcinogenesis in the literature. Even relatively minute doses of arsenicals have occasionally been reported to be followed by typical tumor formation. Widely ranging tissue levels of this element in similar lesions from different patients, and a considerable variation among different specimens taken from the same patient, have been found. The quantity of arsenic present in the tissues appears to bear no precise relationship to the dose and duration of the arsenical exposure and to the lapse of time after the exposure. It has been suggested that the presence of this element in a given specimen cannot be regarded as proof of its having an etiological relationship to the lesion at hand, just as its absence cannot justify its being excluded as a causative factor. A brief review of the pertinent literature is presented.

991 Carcinogenic Risk of Iron-Dextran. Editorial. Brit. Med. J. 1, 1583 (1964).

In 1960 Imferon, a complex of colloidal ferric hydroxide and low molecular weight dextran, was removed from the market following the demonstration of its carcinogenicity in rats, mice and hamsters. Because the experimental doses were large, it was felt that the risk of therapeutic doses was small and the drug was reintroduced. At that time Haddow felt that carcinogenicity could not be excluded until treated patients were followed up for 15 to 20 years. Haddow's recent demonstration of carcinogenicity in rabbits, followed for 4 years, emphasizes again that iron-induced tumors may not appear in man for another decade. Suggestive evidence that iron may be carcinogenic for man is found in the cause of hemochromatosis, in which there is a higher incidence of carcinoma of the liver than with other types of cirrhosis. Iron is readily removed from the injection site in the presence of anemia, and it is possible that this factor, coupled with the use of doses in the therapeutic range, and changing sites of inoculation, will prevent tumor development in man. Hemosiderosis of the liver with anemia is not accompanied by carcinoma. Whether Imferon can induce tumors in anemic animals remains to be determined. With our present state of knowledge Imferon, administered intramuscularly, should be given only for the treatment of resistant anemias when the immediate benefit outweighs possible future carcinogenicity, and for elderly patients when insufficient time would be likely to elapse for development of tumors even if the risks exist.

-- Can. Med. Assn. J. Absts.

992 Toxicological and Biochemical Studies on Some Trialkylgermanium Compounds. Jill E. Cremer and W.N. Aldridge. Brit. J. Ind. Med. 21, 214-217 (July, 1964).

The toxicity of triethyl-and tri-n-butyl-germanium acetates has been studied after their administration to rats. Both compounds had a low toxicity. Triethylgermanium had less than one-tenth of the toxicity of triethyltin or triethyl-lead and, unlike them, it did not appear to have a predominant action on the central nervous system. In biochemical studies in vitro, tri-n-butylgermanium was found to be more active than trimethyl-, triethyl-or tri-n-propyl-germanium in inhibiting both glucose oxidation by slices of rat brain cortex and processes involved in oxidative phosphorylation by rat liver mitochondria. All the germanium compounds tested had less than one-hundredth the activity of the corresponding trialkytin and trialkyl-lead compounds.

-- Authors' abst.

cancer in Connecticut is a significant problem. During the 17 year period of 1935 to 1951 in Connecticut an average of 143 persons died each year from cancer which originated in the mouth. Since that period of time, Connecticut has had its share in population growth and it is fair to assume the current number of deaths caused each year from mouth cancer is now substantially higher. Early detection and early treatment of mouth cancer increases the cure-rates of mouth cancer patients. Since a large percentage of the general population does seek periodic dental care, it is the dentists who are in a particularly advantageous position to play a leading role in early detection of mouth cancer. The new program will be focused on dentists in private practice in Connecticut. Approximately 1,800 in number, this group—more than any other—each year has the best opportunity for providing the largest number of comprehensive mouth examinations in the state. However, the program will definitely not be limited to just dentists in private practice. Also to be invited to participate will be all physicians in the state, including local directors of health, as well as staff members of all hospitals and institutions—especially those caring for the chronically-ill and aged population.

969 Medicinal Arsenic Poisoning and Lung Cancer. A.O. Robson and A.M. Jelliffe. Brit. Med. J. 2, 207-210 (July 27, 1963).

Six cases of bronchogenic carcinoma are reported in patients who had previously developed arsenical skin changes following the therapeutic administration of arsenic. The average interval between the administration of arsenic and the development of cancer was 32 years. All the tumors were anaplastic in type. Although the relationship between the therapeutic administration of arsenic and the later development of lung cancer is unproved, these cases suggest that such a relationship exists. -- Am. Rev. Resp. Dis. Absts.

970 An Index of the Fate of Circulating Cancer Cells. W.I.B. Onuigbo. Lancet 2, 828-831 (Oct. 19, 1963).

Carcinoma of the lung was selected for study because it commonly infiltrates small branches of the pulmonary vein. Metastatic involvement of the renal glomeruli is relatively infrequent, and special attention was focused on this site. One hundred cases of carcinoma of the lung were investigated: a detailed examination of all organs was carried out with a 2- to 3-cm. block from the kidney, which included the capsule, cortex and medulla, and a part of any metastatic lesion present. Of the 100 cases, there was discrete involvement of one or more glomeruli in 10, but there was little difference in the distribution of metastatic lesions in the liver, adrenal, bone, brain, opposite lung, kidney, pancreas, thyroid, spleen, and extra-thoracic muscle, whether or not the renal glomeruli were involved. Because the kidney receives about 25% of the resting cardiac output, many cancer cells must pass through the glomerular capillaries, hence justifying the term "circulating cancer cells." Further investigation of carcinoma metastasis is necessary, and the writer suggests that the blood stream itself should be examined for factors which may determine the fate of the "circulating cancer cells." -- Am. Rev. Resp. Dis. Absts.

971 Bronchogenic Carcinoma in Women. R. Buchberger and R.H. Jenny. Wien. Klin. Wochschr. 75, 718-723 (Oct. 18, 1963). German.

In the last few years the frequency of bronchogenic carcinoma has increased in women as well as in men. Between 1948 and 1960, 120 women were seen with histologically proved bronchogenic carcinoma. Forty-four women underwent resection (20, lobectomies; 24, pneumonectomies), 33 were found inoperable at thoractomy, and 43 were considered inoperable. In the same period of time 974 resections and 445 thoractomies were done in men with histologically proved bronchogenic carcinoma, and 508 men were considered inoperable. In the 1,927 men there were 442 (23%) peripheral tumors; in the 120 women there were 42 (35%) peripheral tumors. Adenocarcinomas were found considerably more frequently in women than in men. The life expectancy of the operated women is slightly better than that of the operated men; the difference is statistically only slightly significant. -- Am. Rev. Resp. Dis. Absts.

of oral cancer detection programs which should include: (1) Education sessions for instructing the dentist as to what constitutes a complete oral examination, including the use of cytology where indicated. (2) Adequate cytology and pathology services for the interpretation of specimens. (3) Consultation service for referring cases for definitive diagnoses and recommendations for treatment. Six references are given. -- Author's summary

853 An Oral Cancer Detection Center. S.J. Shackner. Health News 41, 10-13 (April, 1964).

This paper has attempted to show how an Oral Cancer Detection Center can be set up, how it operates and how it functions. The Center provides a central facility in a rural area for case finding, case referral, and professional and public education in oral cancer detection and control. Through the establishment and operation of similar centers, it is hoped that the profession will be motivated and oriented to utilize the diagnostic aids at its disposal. The private practitioner will become more aware of cancer control and realize the advantages of early detection by doing an oral cancer detection examination whenever a patient visits his office. This will eventually make every office an oral cancer detection center which is the one and only way to conquer the problem of oral cancer. There are 10 references. -- Author's summary

854 The Educational Program for Dentists and Physicians (For Detection of Oral Cancer). M.A. Engelman. Health News 41, 16-19 (April, 1964).

The primary objective of an Oral Cancer Detection Center is the early detection of oral lesions so that the cure rate is increased, the need for disfiguring surgery decreased, and the number of deaths from cancer of this site reduced. A secondary objective of the Center is professional education for dentists and physicians, including residents and internes, stressing thorough oral examinations and exfoliative cytology. A final objective is the education of the general public in the prevention, detection, and treatment of oral cancer. There are 15 references. -- Author's summary

855 Epidemiological Consequences of an Arsenic-Lung Cancer Theory. R.W. Buechley. Am. J. Public Health 53, 1229-1232 (Aug. 1963).

The world-wide lung cancer epidemic associated with cigarette smoking may be explained by an epidemiological chain showing excess lung cancer at each step leading from arsenic-high mines and smelters through arsenical insecticides, to lead arsenate spray residues on cigarette tobacco. If arsenic is a major causative carcinogen, the reported situations are only the known examples of many other situations consequent on the predicted by an arsenic-lung cancer theory. These consequences fall into two classes: (1) Predicted high lung cancer rates should appear in those persons whose work, or residence, is in arsenic-high situations. This list includes miners, smelters, smeltermen's wives and children, insecticide workers, agriculturists using arsenic sprays and processors and users of sprayed products—including cigarette smokers. (2) Lung cancer rates should be lower than one would expect among those whose work, or residence, is in arsenic-low situations no matter what the oth pollutants. This list includes all the populations listed above, given that the mine, smelter, or insecticide is arsenic-free. It also includes cigarette smokers whose smoking is, and has been, confined to arsenic-free tobacco, such as is used in South Africa. -- APCA Absts.

856 A Review of 995 Cases of Primary Carcinoma of the Lung. R. W. Haber. Med. J. Australia 1, 551 (April 11, 1964).

Of 995 cases of carcinoma of the lung reviewed, the anaplastic type was present in nearly 50% and the squamous variety in 38%; 88% of all cases occurred in men. The peak incidence was in the 51 to 70 years age group. More cancers occurred in the right lung than in the left, and more occurred in the upper than in the lower lobes. The prognosis was worse in women and in the aged. It was better for lower lobe cancers in the right lung than for those

vented tube from each engine blows air at very high pressure and forces gravel away from the engine intake.

Other operating problems include temperatures that are 50F to 60F below zero, 60-mph winds, and total darkness in December and January in the High Arctic. Engines on airstrip equipment such as trucks and snowplows are not turned off from Dec. 1 to Mar. 15.

Though the regionals, too, face fuel problems, all are predicting revenue increases this year. They see their biggest growth potential in scheduled passenger service, although no one is scoffing at the big bucks to be made in hauling drilling equipment—and beer—to oil teams in the Arctic or to the off-again, on-again $6-billion James Bay hydroelectric project in northwestern Quebec. Nordair flies there from Montreal, and Quebecair operates cargo-only service.

PWA ships cattle to the Orient and oil-drilling equipment to the Arctic

Cattle plane. In the eyes of many industry observers, Pacific Western is the best run of the regionals. Its fleet consists of seven Boeing 737s, with three more on order, plus two 727s, two long-range 707s, five Convair 640s, four Hercules jet-prop freighters, and a few flying boats. PWA's operations range from its scheduled passenger services to shipping cattle to the Orient and extensive relief work in such places as Nigeria and Bangladesh. Scheduled passenger services account for roughly 65% of PWA's revenues, charters for about 10%, and cargo services for the remaining 25%.

Its cattle plane is typical of PWA's willingness to provide specialized services to meet special needs. A conventional Boeing 707-320C, the plane can be equipped with either 13 stalls holding about 85 1,000-lb. cattle or double tiers of pens that will accommodate a great many more smaller animals. Donald N. Watson, PWA president, says that the plane has carried as many as 700 cattle from Toronto to Athens.

The real keys to profits for PWA and the other regionals, however, have been jets and charters. The jets boosted available seat-miles on routes with good load factors, and the charters gave the carriers the capability to use their aircraft more economically.

Keith Miller, executive vice-president of Eastern Provincial Airways, estimates the seat-mile cost on a 109-passenger 737 at 2.2¢ a mi., compared with 5.5¢ for each mile on the 41-seat Handley Page Heralds the 737s are replacing. The break-even load factor on the jets is 42%, vs. about 80% on the prop planes. "The stimulation of a 737 is very substantial," Miller says. ■

TECHNOLOGY

Industry's latest cancer scare

The deaths of five workers in ten years seem linked to working on the plastic

Federal officials met last week with plastics industry executives in Cleveland and Washington to try to determine whether the industry has unknowingly been exposing some of its 6,500 blue-collar workers to fumes that can lead to a rare form of liver cancer known as angiosarcoma. The focus was on 28 of the 42 plants in the U.S. that make vinyl chloride or use it to produce polyvinyl chloride resin (PVC), one of the most common plastics.

The hearings grew out of the deaths of four workers over the last six years at a B. F. Goodrich Chemical Co. plant in Louisville, Ky. They could ultimately bring costly new rules for the PVC industry, whose resins are used in such items as pipe, floor tile, phonograph records, and latex wall paints. "Improvements in work practices will probably require a 100% increase in the work force," says Walter B. Connolly, Jr., labor counsel for Firestone Tire & Rubber Co., which operates PVC plants in Pottstown, Pa., and Perryville, Md.

In any case, the current PVC hullabaloo is certain to spark new demands by organized labor for closer examination of the possible long-range effects on workers of other industrial chemicals. "The cancer took 15 to 20 years to develop," says one federal epidemiologist. Other chemicals could have similar "latency" periods, he says, so there could be more eruptions in the years ahead. "I hope we're not seeing the beginning of a health collapse."

The vinyl chloride case is not the chemical industry's first encounter with OSHA over carcinogenics. Last May the agency invoked emergency standards for 14 chemicals (BW— May 19, 1973). Final rules for these materials went into effect last week, though. both industry and labor are suing for judicial review.

The prospect of new, petrochemical versions of such health time bombs as "black lung" and mercury poisoning, makes plastic industry leaders shudder. And indeed, new data presented at the standing-room-only OSHA hearing by Italian researcher Cesare Maltoni, of Bologna's Institute of Cancer, leave little doubt that vinyl chloride is carcinogenic—at least to rats. He exposed 67 rats to air containing 250 parts per million of vinyl chloride off and on for 52 weeks. By the end of 127 weeks, Maltoni reported, two had contracted angiosarcoma and nine contracted other forms of cancer. Many chemical industry executives had downgraded the importance of earlier animal test results because the dosages were mas-

A solvent that crippled chemical workers

Last August, Thomas F. Meade, 22, was stricken with a nerve disease after two years of work at Columbus Coated Fabrics Co., a subsidiary of Borden, Inc., in Columbus, Ohio, that makes vinyl-coated fabrics for luggage and wall coverings. The disease, diagnosed as peripheral neuropathy, left Meade crippled, and today he wears leg braces. He is the most severely affected of some 130 workers at the plant who have suffered symptoms of the disease. The lesser symptoms include weakness and loss of coordination.

When the symptoms became widespread last summer, state health officials tested the nerve responses of the plant's 1,124 employees and told 200 of them to stay home for two months. Many others stayed home, too, out of fear. By December, most employees had returned, and many who had showed neuropathic symptoms appeared well again.

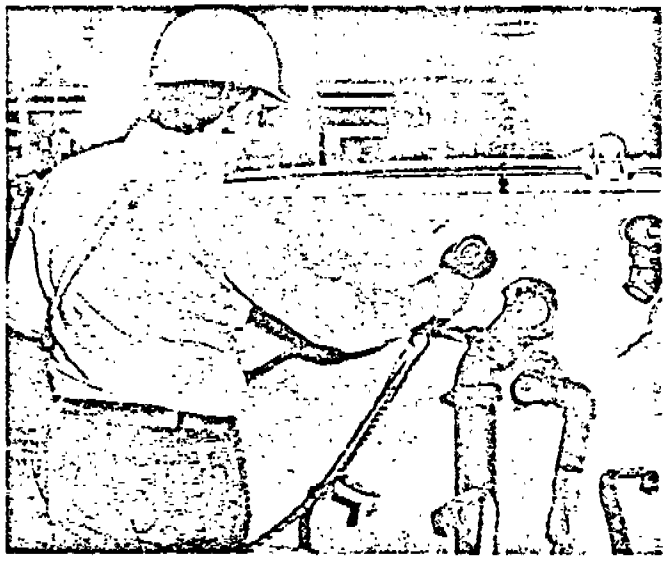
Meanwhile, Ohio health officials had zeroed in on an ink solvent, methyl butyl ketone, used in applying decorative patterns, as the most likely culprit. While continuing to monitor the plant's air, they banned the use of MBK. The plant's managers have switched to a substitute, improved ventilation, issued respirators to print shop workers, and moved lunch areas away from work areas.

But Corwin Smith, president of Local 487 of the Textile Workers Union of America, which represents the plant's workers, is not satisfied. He says that 26 members are still out with the disease, that eight of them are severely crippled, and that three workers whose condition improved are now sick again. On Feb. 9, the local struck the plant as negotiations collapsed on a new contract; one of the union demands was a "proper work environment." Says Smith: "People here don't know whether they will be crippled in the future or not."

sive, on the order to 5,000 to 30,000 ppm.

The bombshell. The cancer crisis hit the vinyl industry just a month ago. Noting an unusual number of liver ailments among the Louisville plant workers, B. F. Goodrich physicians ran blood tests last fall on the 271 workers in the plant's PVC facility and found 55 with apparent liver abnormalities. The company reviewed medical and insurance records and by Jan. 16 had discovered three deaths since 1971 that were attributable to angiosarcoma. Federal health officials estimate the annual death toll in the U.S. from this rare form of cancer at only about 20. On Jan. 29 further review by Goodrich turned up a 1968 death (two more cases, including a 1964 death, were identified this week).

The company's top management had already decided on public disclosure. It reported the situation to the National Institute for Occupational Safety & Health and to the Kentucky Labor Dept. It also began notifying employees in all of its vinyl chloride and PVC operations, and it sent a release to the press. "We are doing our utmost to express our real and serious concern," says John J. Bell, the company's public affairs director, "and yet prevent any undue panic."



A B. F. Goodrich safety inspector uses a chemical "sniffer" to check whether vinyl chloride fumes are leaking from a polymerizing reactor.

NIOSH, which had immediately sent experts to Louisville, held a briefing early last week in Cleveland to tell management and labor leaders in the industry what it knew about the carcinogenic effects of vinyl chloride. And on Friday, many of the same executives showed up in Washington for the OSHA hearing. The federal agency will determine whether the situation warrants either an emergency standard or at least a start on the regular rule-making process.

The attitude of organized labor was a major concern. Anthony Mazzocchi, legislative director of the Oil, Chemical & Atomic Workers, who attended the NIOSH briefing, says: "It's apparent we're dealing with a carcinogen. We want to reduce exposure to zero. But we have a wait-and-see attitude right now."

While the fatalities at Louisville came as a shock to the industry, vinyl chloride has been suspect for a long time. Some 15 years ago Dow Chemical Co., based on its own studies, adopted an average exposure limit of 50 ppm for its workers—well below the 200-ppm limit recommended since 1972 by the American Conference of Government Industrial Hygienists. In 1970, Italian researcher Dr. P. L. Viola reported that rats exposed to heavy doses of vinyl chloride developed malignant tumors. Several European chemical companies banded together to support research by Maltoni, and in the U.S., the Manufacturing Chemists Assn. began to discuss an industry-wide research program. A year ago, the MCA set up an animal test program that will not be completed until late 1975. The association also contracted with Tabershaw-Cooper Associates, of Berkeley, Calif., to check the available death records of workers at other vinyl plants. "So far," says Kenneth Johnson, MCA technical director, "the results haven't been subjected to statistical analysis."

To Dr. Irving J. Selikoff, the history shows that "our approach to the problem was, shall I say, leisurely." Selikoff, director of environmental medicine at New York City's Mount Sinai School of Medicine, has been a frequent critic of industrial health practices, and one chemical executive calls his remark, made at the OSHA meeting, "hindsight."

NIOSH hopes that the cause is a combination of factors at only one plant

Belatedly or not, some PVC producers have been tightening up their operations. Goodrich, for example, says it had already done, or was doing, most of the things NIOSH recommended after visiting the Louisville plant, including sticking to a 50-ppm average exposure limit. "At 50 ppm," says Harry Connors, Jr., general manager of the Plastics Div. of Diamond Shamrock Chemical Co., which also observes that limit, "there are not enough fumes in the air to smell." Where concentrations are higher, he says, "we have ordered our men to wear gas masks."

Vinyl fumes arise partly from leaks in pipes and valves. But another likely source is the polymerization vessels, when they are opened for cleaning and maintenance. NIOSH officials are concentrating now on the polymerization process, but they plan to extend their studies eventually to monomer production, as well as PVC fabrication and even consumer use of PVC products.

Since safe limits for vinyl chloride are unknown, NIOSH is emphasizing safe work practices rather than arbitrary concentration limits. Its recommendations for the Louisville plant, for example, include such things as overhead cleaning, daily showers and clothing changes for workers, and expanded air monitoring.

Pinning it down. Goodrich's Louisville plant uses about 50 different chemicals, and there is no proof of a direct link between vinyl chloride and the liver cancer cases. But NIOSH officials are certain that the link exists, and the MCA's Johnson concedes that "vinyl chloride is the material of primary suspicion." Only two other carcinogens, arsenic and thorium-232, are proven causes of angiosarcoma, and medical records on the four Goodrich workers showed no exposure to either.

Both NIOSH and industry officials hope, though, that the link is peculiar to Goodrich's Louisville plant. Says NIOSH Director Marcus M. Key: "We still hold to the possibility that the cause could be a combination of two or three things acting together in the manufacturing process."

The Louisville plant is Goodrich's oldest PVC plant and, unlike most newer plants, is enclosed. It also has a number of older workers on the line. Some workers may have been affected by an epidemic of hepatitis that swept the city a few years ago. A number of other rubber and chemical plants, and their fumes, are located nearby. And the plant is one of the few that uses vinylidene chloride as a copolymerizing agent. Rudolph Jaeger, a physiologist at the Harvard School of Public Health, told the OSHA meeting that test data appear to point to that chemical, too, as a carcinogen. ■

Chemical Safety Data Sheet SD-56

PROPERTIES AND ESSENTIAL INFORMATION

FOR

SAFE HANDLING AND USE

OF

VINYL CHLORIDE

Chemicals in any form can be safely stored, handled or used if the physical, chemical and hazardous properties are fully understood and the necessary precautions, including the use of proper safeguards and personal protective equipment, are observed.

REVISED 1972

MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N. W. WASHINGTON, D. C. 20009

3. HAZARDS

3.1 HEALTH HAZARDS (See Section 10 MEDICAL MANAGEMENT)

3.1.1 The primary hazard of vinyl chloride is associated with excessive respiratory exposure. Exposure to high levels may produce some lung irritation. Chronic overexposure may produce liver injury. When inhaled it acts primarily as an anesthetic. The odor is pleasant to most individuals and, therefore, acutely dangerous levels may be easily tolerated.

3.1.2 Warning Properties

The lowest concentration of VCM at which its odor can be detected is reported to be 260 ppm. Olfactory fatigue, however, may occur and the sense of smell cannot be relied upon as a warning for excessive low grade exposures.

3.2 FIRE AND EXPLOSION HAZARDS

3.2.1 Vinyl chloride is a gas at normal atmospheric temperature and pressure. The gas will burn very readily in proper mixtures of air or oxygen. An explosion hazard can exist when drawing samples or venting to the atmosphere. Open flames, local hot spots, friction, any spark producing equipment, and static electricity are to be avoided when handling this material.

3.2.2 Combustion Products of Vinyl Chloride Monomer

Analysis of a combustion gas sample obtained immediately above a flame of vinyl chloride monomer burning in air shows presence of hydrogen chloride (27,000 ppm), carbon dioxide (58,000 ppm), carbon monoxide (9,500 ppm) and phosgene less than 10 ppm. Only in the very near vicinity of a VCM fire would significant amounts of phosgene be present.

The main sources of danger to personnel result from the massive formation of hydrogen chloride gas and from carbon monoxide. However, the pungent odor of hydrogen chloride acts as a warning to clear the area or to obtain the necessary breathing apparatus before attempting any fire control measures. See MCA Chemical Safety Data Sheet, SD-39, Hydrochloric Acid (Aqueous) and Hydrogen Chloride (Anhydrous).

3.3 STABILITY HAZARDS

Vinyl chloride is shipped and used in both the inhibited and uninhibited state. In the uninhibited state, high purity must be maintained since contaminants may catalyze polymerization or cause decomposition of the VCM, liberating hydrogen chloride. Prior to shipment, uninhibited VCM should be tested for stability under shipping and storage conditions. Cleanliness of shipping containers is of prime importance when shipping uninhibited VCM.

Vinyl chloride may polymerize as a result of exposure to air, oxygen or sunlight at ambient or higher temperatures.

Vinyl chloride does not form peroxides by autoxidation as readily as many other monomers.

In the absence of an initiator, VCM is chemically quite stable. Commercial VCM, uninhibited, is stored and shipped in steel containers under conditions which avoid exposure to air and sunlight. For large volume, long term storage, refrigeration is sometimes employed to maintain the temperature at about 20° C., maximum, to minimize the formation of haze, a condition caused by a small degree of polymerization.

4. ENGINEERING CONTROL OF HAZARDS

4.1 BUILDING DESIGN

Equipment and vessels containing VCM should preferably be isolated from other facilities by walls and floors of fire resistive construction.

Standard fire walls are recommended for the isolation of larger equipment and storage tanks, while partitions of plaster on expanded metal lath may be used to isolate smaller equipment from other combustible materials.

Not less than two means of exit should be provided from each separate room or building in which VCM is stored, handled or used. No portions of such a room or building should be farther than 75 feet from the nearest exit. Additional exits should be provided depending upon the number of persons in the building. (See NFPA Standard #101 Life Safety Code.)

All exit doors should open out in the direction of travel and should be provided with panic hardware. Fire doors should open out in the direction of travel and be of an approved type.

Operations where large quantities of VCM are used should preferably be housed in one story buildings.

available to man the lifeline and to assist in the rescue if needed. The rescuer should be in view of the outside attendant at all times or in voice communication with him.

8.5 EXTERIOR REPAIR WORK

All outside welding, burning or spark-producing work on tanks or equipment which have contained VCM should be done after the container has been thoroughly cleaned of VCM vapors. Purging should be tested by a competent person to see if it is free of VCM. It is not recommended that air be used to purge a vessel.

If the repair work is interrupted, the tank atmosphere should be checked thoroughly and a new work permit issued before resumption of work.

9. WASTE DISPOSAL (See 7.5)

9.1 All Federal, State, and Local regulations regarding health and pollution should be observed. Disposal of waste material, however, depends to a great extent upon surroundings, weather conditions and the emergency making disposal necessary.

9.2 When it becomes necessary to dispose of VCM as such, it is preferable to do so as a vapor, venting to an area free of any source of ignition.

9.3 When a waste disposal problem arises as a result of a major spill or equipment rupture, only properly protected and qualified personnel should remain in the area.

9.4 Waste mixtures containing VCM should not be allowed to enter drain or sewers as serious explosions in such systems may result.

10. MEDICAL MANAGEMENT

10.1 HEALTH HAZARDS

10.1.1 Vinyl chloride monomer does not present a serious industrial health hazard provided workers are adequately supervised and observe the proper means of handling it. Under the Occupational Safety and Health Act, the U.S. Department of Labor has set a 500 ppm Ceiling Value on permitted employee exposures. Based upon animal and human observations, this level provides considerable margin of safety for industrial exposures.

NOTE: A syndrome termed occupational acro-osteolysis, characterized primarily by Raynaud's phenomenon and osteolytic changes in certain bones, particularly the distal phalanges of the hands, has been noted among certain workers in vinyl chloride polymerization operations. The specific cause of this disease, and particularly any role played by vinyl chloride, is unknown.

Recent research studies reported from Italy indicate that repeated, long-term high level exposures of rats to vinyl chloride monomer vapor can result in the development of malignant tumors. However, many years of industrial experience with human exposures to concentrations frequently far above current standards have not demonstrated any carcinogenicity to humans.

10.1.2 Acute Toxicity

Levels on the order of 6,000 ppm for five minutes exposure are required to produce minimal symptoms resembling mild alcohol intoxication in humans. Levels approximately 16,000 ppm for the same length of time will produce varying degrees of intoxication, with light-headedness, some nausea, and a dulling of visual and auditory responses in most humans.

10.1.3 Chronic Toxicity

The liver is the principal target resulting from excessive chronic exposure. The currently recommended ceiling level (OSHA) of 500 ppm is well below a level producing any signs or symptoms of toxicity.

10.2 PREVENTIVE MEASURES

10.2.1 All operations in which vinyl chloride is used should be regularly evaluated and atmospheric concentrations kept, at all times, below 500 ppm. Sophisticated air sampling techniques are required. This includes gas chromatography. Processes must be closed or ventilated sufficiently to achieve a concentration control low enough so that respiratory protection devices are needed only on an emergency basis.

10.2.2 Personal Hygiene

Vinyl chloride should be kept off the skin and out of contact with the eyes. If accidental contact to the skin occurs, immediate washing with soap and water is necessary; if to the eyes, immediate irrigation

for a minimum of 15 minutes with water is required. The pesence of skin and eye washing equipment in the areas where vinyl chloride is used is necessary.

Washing supplies and equipment should be maintained and always immediately available.

10.2.3 Physical Examinations

Preplacement examinations should be made on all workers having potential exposure to vinyl chloride, with particular emphasis placed upon liver and kidney functions.

10.3 SUGGESTIONS TO PHYSICIANS

Treatment for vinyl chloride intoxication is symptomatic; no special procedures are required. It should be recognized that the principal target of chronic exposures is the liver, with secondary effects, particularly in acute exposures, to the kidney. In acute overexposures the primary effect is on the central nervous system.

NOTE TO PHYSICIAN: Avoid use of epinephrine or related drugs in treating acute overexposure cases since vinyl chloride may sensitize the heart to the arrhythmic action of these drugs.

10.3.1 Oxygen Administration

Oxygen has been found useful in the treatment of inhalation exposures of many chemicals, especially those capable of causing either immediate or delayed harmful effects in the lungs.

In most exposures, administration of 100% oxygen at atmospheric pressures has been found to be adequate. This is best accomplished by use of a face mask having a reservoir bag of the non-rebreathing type. Inhalation of 100% oxygen should not exceed one hour of continuous treatment. After each hour, therapy may be interrupted. It may be reinstituted as the clinical condition indicates.

Some believe that superior results are obtained when exposures to lung irritants are treated with oxygen under an exhalation pressure not exceeding 4 cm. water. Masks providing for such exhalation pressures are obtainable. A single treatment may suffice for minor exposures to irritants. It is believed by some observers that oxygen under pressure is useful as an aid in the prevention of pulmonary edema after breathing irritants.

In the event of an exposure causing symptoms or in case of a history of severe exposure, the patient may be treated with oxygen under 4 cm. exhalation pressure for one-half hour periods out of every hour. Treatment may be continued in this way until symptoms subside or other clinical indications for interruption appear.

CAUTION: It may not be advisable to administer oxygen under positive pressure in the presence of impending or existing cardiovascular failure. The use of adrenalin is not recommended because some chlorinated hydrocarbons can increase the risk of ventricular fibrillation after adrenalin therapy.

11. FIRST AID

11.1 GENERAL PRINCIPLES

First aid should be started at once in case of acute intoxication with vinyl chloride. Immediately remove the affected individual to fresh air. Refer all injured individuals to a physician and give a detailed account of the incident.

11.2 CONTACT WITH SKIN AND MUCOUS MEMBRANES

Vinyl chloride, in concentrated form, is a skin irritant. All contaminated clothing should be removed at once: and this clothing, including shoes, if there is any evidence of contamination, should not be worn again until thoroughly dry. All affected skin areas should be thoroughly washed with warm water and soap. The individual should be referred to a physician.

11.3 CONTACT WITH EYES

If vinyl chloride has entered the eyes, prompt washing with copious quantities of water for at least 15 minutes should be instituted immediately. It is advisable to irrigate the eyes gently with water at room temperature in order to minimize additional pain and discomfort. Prompt medical attention should be obtained.

11.4 INHALATION

Promptly remove the affected individual from exposure, to fresh air. If breathing has ceased effective artificial respiration should be started immediately. If oxygen inhalation equipment is available oxygen should be administered, provided a person authorized for such administration by a physician is available. The patient should be comfortably warm but not hot. Stimulants will rarely be necessary where adequate oxygenation is maintained. Any such drugs for shock treatment should be given only by the attending physician. *Never attempt to give anything by mouth to an unconscious patient.*

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

SURVEY OF COMPOUNDS WHICH HAVE BEEN TESTED FOR CARCINOGENIC ACTIVITY

Supplement 1

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Reference	Animal	Strain or type	Sex	Preparation and dose	Site and route	Animals with tumors	Survival	Duration of experiment
240.--VINYL CHLORIDE POLYMER $-(CH_2CHCl)_x-$								
Oppenheimer et al., 1952	45 rats	Wistar	----	Film	S.C.	Tumors[238]	44 alive at 189 d.	Over 22 mos.
247.--VINYL PROPIONATE $CH_3CH_2COOCH=CH_2$								
Ambrose, 1950a	5 rats	Albino	F	0.64% in the diet	P.O.	0	----	392 d.
	45 rats	Albino	F	0.05 - 2.56%	P.O.	0	----	223 d.
248.--ZINC DIMETHYLDITHIOCARBAMATE $Zn[-S-CS-N(CH_3)_2]_2$								
Hodge et al., 1952a	Dogs	----	----	5 or 25 mg. per kg. by capsule daily for 1 mo.	P.O.	0	100%	1 mo.
	40 rats	Rochester	M&F	0.01 - 0.5% in the diet	P.O.	0	----	1 mo.
249.--ZINC ETHYLENE BISDITHIOCARBAMATE[239] $(CH_2)_2(NH-CS-S-)_2Zn$								
Smith, Jr., et al., 1953	200 rats	Albion	M&F	500 - 10,000 p.p.m. in the diet	P.O.	0[240]	Sacrificed at various intervals	30 d.
	100 rats	Albino	M&F	500 - 10,000 p.p.m. in the diet	P.O.	0[241]	13 died by 52 wks.	2 yrs.
	9 dogs	Mongrel	----	20 - 10,000 p.p.m. in the diet	P.O.	0[242]	100%	1 yr.

[238] 14 sarcomas, 12 fibrosarcomas, 1 liposarcoma, 1 unclassified malignancy. First tumor at 189 days.

[239] Marketed as Dithane Z78.

[240] 10 rats at the 10,000 p.p.m. level had thyroid hyperplasia.

[241] 9 lung tumors, 1 adrenal tumor, 1 small bowel tumor, 1 mammary carcinoma and 1 adenocarcinoma of thyroid in 100 treated rats. Considered spontaneous. 2 lung tumors in 20 controls.

[242] 10,000 p.p.m. induced thyroid hyperplasia.